Access DB# 137240

SEARCH REQUEST FORM

Scientific and Technical Information Center

Requester's Full Name: Mike Meller Examiner #: 69404 Date: 11/4/04
Art Unit: 1654 Phone Number: 571-272-0967 Serial Number: 09/937,306
Mail Box and Bldg Room Location: Mailbox: Rem 3C18 Results Format Preferred (circle): PAPER DISK E-MAIL

If more than one search is submitted, please prioritize searches in order of need.

Please provide a detailed statement of the search topic, and describe as specifically as possible the subject matter to be searched. Include the elected species or structures, keywords, synonyms, acronyms, and registry numbers, and combine with the concept or utility of the invention. Define any terms that may have a special meaning. Give examples or relevant citations, authors, etc., if known. Please attach a copy of the cover sheet, pertinent claims, and abstract.

Title of Invention: Combination of NO synthase inhibitors and metabolic antioxidants

Inventors (please provide full names): Michel Auguet, Jeremiah Harnett, Pierre-Etienne Chabrier de Lassauniere

Earliest Priority Filing Date: 4/2/99

For Sequence Searches Only Please include all pertinent information (parent, child, divisional, or issued patent numbers) along with the appropriate serial number.

Please search lipoic acid and N-phenyl-2-thiophenecarboximidamine.

~~Search them in separate containers or together but~~

Search them together, but they must be separate from one another, not in the same composition/container

for example: separate containers, separate pills etc.

*If I can't find, search other inhibitor substances & antioxidant substances i.e. see claims 4, 8, 9, 10.

STAFF USE ONLY

Searcher: Beverly C2528	NA Sequence (#)	STN ✓
Searcher Phone #:	AA Sequence (#)	Dialog
Searcher Location	Structure (#)	Questel/Orbit
Date Searcher Picked Up	Bibliographic	Dr. Link
Date Completed	Litigation	Lexis/Nexis
Searcher Prep & Review Time	Fulltext	Sequence Systems
Clerical Prep Time	Patent Family	WWW/Internet
Online Time	Other	Other (specify)

PTO-1590 (8-01)

Meller
09/937306


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     FILE 'REGISTRY' ENTERED AT 11:47:26 ON 05 NOV 2004
                E LIPOIC ACID/CN 5
L1             2 S E3
                E "N-PHENYL-2-THIOPHENCARBOXIMIDAMINE"/CN 5
                E "N-PHENYL-2-THIOPHENECARBOXIMIDAMINE"/CN 5
                E "N-PHENYL-2-THIOPHENE CARBOXIMIDAMINE"/CN 5

                E "N-PHENYL-2-THIOPHENE-CARBOXIMIDAMINE"/CN 5

     FILE 'CAPLUS' ENTERED AT 11:54:47 ON 05 NOV 2004
L1             2 SEA FILE=REGISTRY ABB=ON  PLU=ON  "LIPOIC ACID"/CN
L2          3850 SEA FILE=CAPLUS ABB=ON  PLU=ON  L1 OR LIPOIC OR THIOCTIC
L3             1 SEA FILE=CAPLUS ABB=ON  PLU=ON  (PHENYL OR PH)(1W)(THIOPHENECAR
                  BOXIMIDAMINE OR THIOPHENE CARBOXIMIDAMINE)
L4             1 SEA FILE=CAPLUS ABB=ON  PLU=ON  L2 AND L3

L4   ANSWER 1 OF 1  CAPLUS  COPYRIGHT 2004 ACS on STN
ED   Entered STN:  13 Oct 2000
ACCESSION NUMBER:          2000:725417  CAPLUS
DOCUMENT NUMBER:           133:276363
TITLE:                     Association of NO-synthase inhibitors and metabolic
                           antioxidants
INVENTOR(S):               Auguet, Michel; Harnett, Jeremiah; Chabrier De
                           Lassauniere, Pierre-etienne
PATENT ASSIGNEE(S):        Societe de Conseils de Recherches et d'Applications
                           Scientifiques (S.C.R.A.S, Fr.
SOURCE:                    PCT Int. Appl., 16 pp.
                           CODEN: PIXXD2
DOCUMENT TYPE:             Patent
LANGUAGE:                  French
FAMILY ACC. NUM. COUNT:    1
PATENT INFORMATION:

     PATENT NO.            KIND   DATE        APPLICATION NO.          DATE
     ----------            ----   --------    ---------------------    --------
     WO 2000059448          A2    20001012    WO 2000-FR812            20000331
     WO 2000059448          A3    20010308
         W:  AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR,
             CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU,
             ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU,
             LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE,
             SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA,
             ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
         RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE,
             DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF,
             CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG
     FR 2791571             A1    20001006    FR 1999-4134             19990402
     FR 2791571             B1    20021004
     EP 1169005             A2    20020109    EP 2000-915262           20000331
         R:  AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT,
             IE, SI, LT, LV, FI, RO
     NO 2001004770          A     20011123    NO 2001-4770             20011001
PRIORITY APPLN. INFO.:                        FR 1999-4134         A   19990402
                                              WO 2000-FR812        W   20000331
AB   The invention relates to a pharmaceutical composition comprising as an
active
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Searcher : Shears 571-272-2528

ingredient one or several substances interfering with the synthesis of nitrogen monoxide by inhibiting NO-synthase and one or several metabolic antioxidants containing thiol groups and intervening in the redox status of the thiol groups, and optionally a pharmaceutically acceptable support. The invention also relates to a product containing one or several NO-synthase inhibitors and one or several metabolic antioxidants intervening in the redox status of the thiol groups, as a combined product in a separated form of said active ingredients. A mixture of 3 mg/kg N-**phenyl**-2-**thiophenecarboximidamine** and 10 mg/kg **lipoic** acid increased the dopamine level in guinea pigs suffering from parkinson to 5.21 ng/mg nervous tissue which was higher than either compds.

IT **57828-26-9, Lipoic** acid **57828-26-9D, Lipoic** acid, derivs.
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(association of NO-synthase inhibitors and metabolic antioxidants)

(FILE 'MEDLINE, BIOSIS, EMBASE, WPIDS, CONFSCI, SCISEARCH, JICST-EPLUS, JAPIO' ENTERED AT 11:58:25 ON 05 NOV 2004)
L5 1 S L4

L5 ANSWER 1 OF 1 WPIDS COPYRIGHT 2004 THE THOMSON CORP on STN
ACCESSION NUMBER: 2000-647288 [62] WPIDS
DOC. NO. CPI: C2000-195823
TITLE: Compositions containing nitrogen monoxide synthase inhibitor and dithiol having metabolic antioxidant activity, useful for treating cardio and cerebrovascular disorders, inflammatory disorders or auto-immune diseases.
DERWENT CLASS: B05
INVENTOR(S): AUGUET, M; CHABRIER DE LASSAUNIERE, P E; HARNETT, J; CHABRIER DE LASSAUNIERE, P
PATENT ASSIGNEE(S): (SCRC) SCRAS SOC CONSEILS RECH & APPL SCI
COUNTRY COUNT: 93
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
WO 2000059448	A2	20001012	(200062)*	FR	15
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW NL OA PT SD SE SL SZ TZ UG ZW					
W: AE AG AL AM AT AU AZ BA BB BG BR BY CA CH CN CR CU CZ DE DK DM DZ EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT TZ UA UG US UZ VN YU ZA ZW					
FR 2791571	A1	20001006	(200062)		
AU 2000036637	A	20001023	(200107)		
EP 1169005	A2	20020109	(200205)	FR	
R: AL AT BE CH CY DE DK ES FI FR GB GR IE IT LI LT LU LV MC MK NL PT RO SE SI					
NO 2001004770	A	20011123	(200207)		
JP 2002541077	W	20021203	(200309)		26

Searcher : Shears 571-272-2528

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 2000059448	A2	WO 2000-FR812	20000331
FR 2791571	A1	FR 1999-4134	19990402
AU 2000036637	A	AU 2000-36637	20000331
EP 1169005	A2	EP 2000-915262	20000331
		WO 2000-FR812	20000331
NO 2001004770	A	WO 2000-FR812	20000331
		NO 2001-4770	20011001
JP 2002541077	W	JP 2000-609013	20000331
		WO 2000-FR812	20000331

FILING DETAILS:

PATENT NO	KIND	PATENT NO
AU 2000036637	A Based on	WO 2000059448
EP 1169005	A2 Based on	WO 2000059448
JP 2002541077	W Based on	WO 2000059448

PRIORITY APPLN. INFO: FR 1999-4134 19990402

AN 2000-647288 [62] WPIDS

AB WO 200059448 A UPAB: 20001130

NOVELTY - Pharmaceutical compositions contain:

(1) one or more substances that inhibit nitrogen monoxide (NO) synthase;

(2) one or more substances having metabolic antioxidant activity containing at least two thiol groups intervening in the redox status of thiol groups; and

(3) optionally a pharmaceutical carrier.

DETAILED DESCRIPTION - An INDEPENDENT CLAIM is also included for a product containing the different substances in separated forms.

ACTIVITY - Antimigraine; hypotensive; cardiant; vasotropic; thrombolytic; antibacterial; immunosuppressive; antiemetic; cytostatic; neuroprotective; analgesic; antialcoholic; antidepressive; neuroleptic; anticonvulsant; anabolic; antiarteriosclerotic; ophthalmological; antipsoriatic; antirheumatic; antiarthritic; antiviral; anti-HIV; antidiabetic. Mice were injected intraperitoneally three times at 2 hourly intervals with 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) (15-20 mg/kg). This induced Parkinson-like symptoms resulting from degeneration of dopaminergic nigrostriatal neurones. The products under test were given orally 90 minutes before each MPTP injection and 90 minutes after the last one. The animal were sacrificed after 24 hours and level of dopamine in the striatum was measured. Group 1 received no test compounds, Group 2 received N-**phenyl**-2-**thiophene carboximidamine** alone (3 mg/kg), Group 3 received reduced **lipoic** acid alone (10 mg/kg), and Group 4 received N-**phenyl**-2-**thiophene carboximidamine** (3 mg/kg) plus reduced **lipoic** acid (10 mg/kg). The dopamine levels were as follows: Group 1 - 3.24 ng/mg; Group 2 -3.77 ng/mg; Group 3 - 3.81 ng/mg; Group 4 - 5.21 ng/mg. These results show that only when both active materials are given is the neurotoxicity of MPTP effectively countered.

MECHANISM OF ACTION - NO synthase inhibitors and metabolic antioxidants.

Searcher : Shears 571-272-2528

USE - The compositions are useful for treating cardiovascular and cerebrovascular disorders such as migraine, hypertension, cardiac or cerebral infarctus, ischemias or thromboses, septic shock, radioactive irradiation, solar irradiation, organ transplants, central and peripheral nervous system disorders such as neurodegenerative diseases, pain, trauma, drug or alcohol dependence, erectile and reproductive disorders, cognitive disorders, depression, schizophrenia, epilepsy, or sleep or eating disorders, proliferative and inflammatory disorders such as cancers, atherosclerosis, cataracts, psoriasis, and rheumatoid arthritis, viral and auto-immune diseases such as lupus or AIDS, diabetes and its complications, autosomal genetic disorders, and any disorder characterized by production or dysfunctioning of nitrogen monoxide or implicating the redox status of thiols.
Dwg.0/0

FILE 'REGISTRY' ENTERED AT 11:59:54 ON 05 NOV 2004
L6 4 S (DITHIOTHREITOL OR PYRITINOL OR PENICILLAMINE OR "N-ACETYLCYS
L7 3 S ("L-NITRO-ARGININE" OR "L-NITRO-ARGININE METHYL ESTER" OR "L-
L8 1 S ("1,2-(TRIFLUOROMETHYLPHENYL-PHENYL)IMIDAZOLE" OR "1-AMINO-4-
E ("S-ETHYLISOTHIOUREA" OR "S-METHYL-L-THIOCITRULLINE" OR "S-ET
L9 3 S ("S-ETHYLISOTHIOUREA" OR "S-METHYL-L-THIOCITRULLINE" OR "S-ET
L10 7 S L7 OR L8 OR L9

FILE 'CAPLUS' ENTERED AT 12:06:50 ON 05 NOV 2004
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L3 1 SEA FILE=CAPLUS ABB=ON PLU=ON (PHENYL OR PH)(1W)(THIOPHENECAR BOXIMIDAMINE OR THIOPHENE CARBOXIMIDAMINE)
L6 4 SEA FILE=REGISTRY ABB=ON PLU=ON (DITHIOTHREITOL OR PYRITINOL OR PENICILLAMINE OR "N-ACETYLCYSTEINE")/CN
L7 3 SEA FILE=REGISTRY ABB=ON PLU=ON ("L-NITRO-ARGININE" OR "L-NITRO-ARGININE METHYL ESTER" OR "L-MONOMETHYLARGININE" OR AMINOGUANIDINE OR AGMATINE OR "2-AMINO-1-(METHYLAMINO)BENZIMIDAZOLE" OR "5-NITRO-INDAZOLE" OR "6-NITRO-INDAZOLE" OR "7-NITRO-INDAZOLE" OR "1,2-(TRIFLUORMETHYLPHENYL)PHENYL-IMIDAZOLE")/CN
L8 1 SEA FILE=REGISTRY ABB=ON PLU=ON ("1,2-(TRIFLUOROMETHYLPHENYL-PHENYL)IMIDAZOLE" OR "1-AMINO-4-METHYL-6-(2-AMINOETHYL)PYRIDINE" OR "2-IMINOPIPERIDINE" OR "2-IMINOHOMOPIPERIDINE" OR "2-IMINO-5,6-DIHYDRO-1,3-THIAZINE" OR "2-IMINO-5,6,-DIHYDRO-1,3-OXAZINE" OR "2-IMINOTETRAHYDROPYRIMIDINE")/CN
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L10 7 SEA FILE=REGISTRY ABB=ON PLU=ON L7 OR L8 OR L9
L11 27661 SEA FILE=CAPLUS ABB=ON PLU=ON L6 OR DI(W)(THIOTHREITOL OR THIO THREITOL) OR DITHIO THREITOL OR DITHIOTHREITOL OR PYRITINOL OR PENICILLAMINE OR N(W)(ACETYLCYSTEIN# OR (AC OR ACETYL)(W)CYSTEIN#)
L12 31164 SEA FILE=CAPLUS ABB=ON PLU=ON L2 OR L11
L13 9161 SEA FILE=CAPLUS ABB=ON PLU=ON L10 OR (MONOMETHYL OR MONO(W)(ME OR METHYL) OR NITRO)(W)(ARG OR ARGININE) OR NITROARGININE OR MONOMETHYLARGININE OR MONO METHYLARGININE OR AMINOGUANIDINE OR AMINO GUANIDINE OR AGMATINE OR AMINO(W)(METHYLAMINO? OR (METHYL OR ME)(W)AMINO?) OR (5 OR 6 OR 7)(W)NITRO INDAZOLE
L14 105 SEA FILE=CAPLUS ABB=ON PLU=ON 1(W)2(W)(TRIFLUOROMETHYLPHENYL? OR TRI(W)(FLUOROMETHYLPHENYL? OR FLUORO(W)(METHYLPHENYL? OR (ME OR METHYL)(W)(PHENYL? OR PH)) OR FLUOROMETHYL(W)(PHENYL?

OR PH)))
L15 1 SEA FILE=CAPLUS ABB=ON PLU=ON 2(W)AMINO(W)4(W)(METHYL OR ME)(W)6(W)2(W)(AMINOETHYL? OR AMINO(W)(ETHYL? OR ET))
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L17 75 SEA FILE=CAPLUS ABB=ON PLU=ON S(W)(METHYL OR ME OR ETHYL OR ET)(1W)(THIOCITRULLINE OR THIO CITRULLINE) OR 2(W)(IMINOTETRAHYDROPYRIMIDINE OR IMINO(W)(TETRAHYDROPYRIMIDINE OR TETRA(W)(HYDROPYRIMIDINE OR HYDRO PYRIMIDINE) OR TETRAHYDRO PYRIMIDINE) OR IMINOTETRAHYDRO PYRIMIDINE)
L19 9389 SEA FILE=CAPLUS ABB=ON PLU=ON L3 OR L13 OR L14 OR L15 OR L16 OR L17
L20 166 SEA FILE=CAPLUS ABB=ON PLU=ON L12 AND L19
L21 9 SEA FILE=CAPLUS ABB=ON PLU=ON L20 AND (SEP## OR SEPARAT?)

L22 8 L21 NOT L4

L22 ANSWER 1 OF 8 CAPLUS COPYRIGHT 2004 ACS on STN
ED Entered STN: 23 Jul 2004
ACCESSION NUMBER: 2004:589018 CAPLUS
DOCUMENT NUMBER: 141:128475
TITLE: Reduction of hair growth with compositions containing for example α-difluoromethylornithine
INVENTOR(S): Styczynski, Peter; Passi, Rajeev Kumar; Ahluwalia, Gurpreet S.; Shander, Douglas
PATENT ASSIGNEE(S): USA
SOURCE: U.S. Pat. Appl. Publ., 15 pp.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2004141935	A1	20040722	US 2003-347987	20030121
WO 2004064749	A2	20040805	WO 2004-US1420	20040120
WO 2004064749	A3	20040910		

W: AE, AE, AG, AL, AL, AM, AM, AM, AT, AT, AU, AZ, AZ, BA, BB, BG, BG, BR, BR, BW, BY, BY, BZ, BZ, CA, CH, CN, CN, CO, CO, CR, CR, CU, CU, CZ, CZ, DE, DE, DK, DK, DM, DZ, EC, EC, EE, EE, EG, ES, ES, FI, FI, GB, GD, GE, GE, GH, GM, HR, HR, HU, HU, ID, IL, IN, IS, JP, JP, KE, KE, KG, KG, KP, KP, KP, KR, KR, KZ, KZ, KZ, LC, LK, LR, LS, LS, LT, LU, LV, MA, MD, MD, MG, MK, MN, MW, MX, MX, MZ, MZ, NA, NI

PRIORITY APPLN. INFO.: US 2003-347987 A2 20030121
AB Hair growth can be reduced by topical application of a composition including an emulsion and a compound that inhibits hair growth, e.g., an ornithine decarboxylase inhibitor, α-difluoromethylornithine (DFMO). The emulsion (1) is prepared using a phase inversion procedure, (2) includes

droplets having an average size of from 10 nm to 150 nm, (3) includes droplets sufficiently small that the composition is clear, (4) is in the form of a nanoemulsion, and/or (5) is an oil-in-water emulsion in which the compound that inhibits hair growth is dissolved in the water phase and the oil phase includes glyceryl isostearate. For example, a composition contained (by weight) DFMO 1.00%, glycerol 3.00%, Isoceteth-20 4.60%, glyceryl isostearate 2.40%, bis(2-ethylhexyl) carbonate 5.00%, preservative, fragrance and color as needed, and water to 100.00%.

IT **52-67-5**, D-**Penicillamine 616-91-1**, N-Acetyl-L-cysteine **17035-90-4**
RL: COS (Cosmetic use); BIOL (Biological study); USES (Uses)
(topical compns. for hair growth inhibitors)

L22 ANSWER 2 OF 8 CAPLUS COPYRIGHT 2004 ACS on STN
ED Entered STN: 01 Feb 2002
ACCESSION NUMBER: 2002:90556 CAPLUS
DOCUMENT NUMBER: 136:131255
TITLE: Methods for early diagnosis of kidney disease and treatment by drug intervention using lysosome activating compounds
INVENTOR(S): Comper, Wayne D.
PATENT ASSIGNEE(S): Austria
SOURCE: U.S. Pat. Appl. Publ., 30 pp., Cont.-in-part of U.S. Ser. No. 415,217.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 4
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2002012906	A1	20020131	US 2001-893346	20010628
US 2002110799	A1	20020815	US 1999-415217	19991012
US 6447989	B2	20020910		
WO 2000037944	A1	20000629	WO 1999-IB2029	19991220
W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
ZA 2001005058	A	20020620	ZA 2001-5058	20010620
US 2004106155	A1	20040603	US 2003-721351	20031126

PRIORITY APPLN. INFO.:

AU 1998-7843	A	19981221
US 1999-415217	A2	19991012
WO 1999-IB2029	W	19991220
US 2001-893346	A1	20010628

AB A method is disclosed for diagnosing early stage of a disease in which an intact protein found in urine is an indicator of the disease, followed by early drug intervention to prevent and treat the disease are also

disclosed. The drug treatment involves the use of a lysosome activating compound Urine samples of normal and diabetic patients were analyzed by size-exclusion chromatog. and HPLC.

IT **79-17-4, Aminoguanidine**
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(as lysosome-activating compds.; methods for early diagnosis of kidney disease and treatment by drug intervention using lysosome activating compds.)

IT **52-67-5, Penicillamine**
RL: ADV (Adverse effect, including toxicity); BIOL (Biological study)
(kidney disease from; methods for early diagnosis of kidney disease and treatment by drug intervention using lysosome activating compds.)

L22 ANSWER 3 OF 8 CAPLUS COPYRIGHT 2004 ACS on STN
ED Entered STN: 05 Nov 1999
ACCESSION NUMBER: 1999:705483 CAPLUS
DOCUMENT NUMBER: 132:46761
TITLE: Essential Thiol Requirement To Restore Pterin- or Substrate-Binding Capability and To Regenerate Native Enzyme-Type High-Spin Heme Spectra in the Escherichia coli-Expressed Tetrahydrobiopterin-Free Oxygenase Domain of Neuronal Nitric Oxide Synthase
AUTHOR(S): Sono, Masanori; Ledbetter, Amy P.; McMillan, Kirk; Roman, Linda J.; Shea, Thomas M.; Masters, Bettie Sue Siler; Dawson, John H.
CORPORATE SOURCE: Department of Chemistry and Biochemistry and School of Medicine, University of South Carolina, Columbia, SC, 29208, USA
SOURCE: Biochemistry (1999), 38(48), 15853-15862
CODEN: BICHAW; ISSN: 0006-2960
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Nitric oxide (NO) synthases (NOS) are thiolate-ligated heme-, tetrahydrobiopterin (BH4)-, and flavin-containing monooxygenases which catalyze the NADPH-dependent conversion of L-arginine (L-Arg) to NO and citrulline. NOS consists of two domains: an N-terminal oxygenase (heme- and BH4-bound) domain and a C-terminal reductase (FMN- and FAD-bound) domain. In this study, we have spectroscopically examined the binding of L-Arg and BH4 to the dimeric, BH4-free ferric neuronal NOS (nNOS) oxygenase domain expressed in Escherichia coli **sep.** from the reductase domain. Addition of L-Arg or its analog inhibitors (NG-methyl-L-Arg, NG-nitro-L-Arg) and BH4, together with **dithiothreitol** (DTT), to the pterin-free ferric low-spin oxygenase domain (λmax: 419, 538, 568 nm) and incubation for 2-3 days at 4 °C converted the domain to a native enzyme-type, predominantly high-spin state (λmax: .apprx.395, .apprx.512, .apprx.650 nm). 7,8-Dihydrobiopterin and other thiols (e.g., β-mercaptoethanol, cysteine, and glutathione, with less effectiveness) can replace BH4 and DTT, resp. The UV-visible absorption spectrum of L-Arg-bound ferric full-length nNOS, which exhibits a relatively intense band at .apprx.650 nm (ε = 7.5-8 mM-1 cm-1) due to the presence of a neutral flavin semiquinone, can then be quant. reconstructed by combining the spectra of equimolar amts. of the oxygenase and reductase domains. Of particular note, the heme spin-state conversion does not occur in the absence of a thiol even after prolonged (35-48 h) incubation of the oxygenase domain

with BH4 and/or L-Arg under anaerobic conditions. Thus, DTT (or other thiols) plays a significant role(s) beyond keeping BH4 in its reduced form, in restoring the pterin- and/or substrate-binding capability of the E. coli-expressed, BH4-free, dimeric nNOS oxygenase domain. Our results in combination with recently available X-ray crystallog. and site-directed mutagenesis data suggest that the observed DTT effects arise from the involvement of an inter-subunit disulfide bond or its rearrangement in the NOS dimer.

IT **17035-90-4**, L-NG-Methylarginine
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(binding; essential thiol requirement for pterin- or substrate-binding and to regenerate native enzyme-type high-spin heme spectra in the tetrahydrobiopterin-free oxygenase domain of neuronal nitric oxide synthase)

IT **3483-12-3, Dithiothreitol**
RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(essential thiol requirement for pterin- or substrate-binding and to regenerate native enzyme-type high-spin heme spectra in the tetrahydrobiopterin-free oxygenase domain of neuronal nitric oxide synthase)

REFERENCE COUNT: 61 THERE ARE 61 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L22 ANSWER 4 OF 8 CAPLUS COPYRIGHT 2004 ACS on STN
ED Entered STN: 21 Mar 1998
ACCESSION NUMBER: 1998:169475 CAPLUS
DOCUMENT NUMBER: 128:248580
TITLE: Association of NO synthase inhibitors with trappers of reactive oxygen species
INVENTOR(S): Chabrier De Lassauniere, Pierre-Etienne; Bigg, Denis
PATENT ASSIGNEE(S): Societe De Conseils De Recherches Et D'applications Scientifiques (S.C.R.A.S, Fr.
SOURCE: PCT Int. Appl., 22 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: French
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9809653	A1	19980312	WO 1997-FR1567	19970905
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
FR 2753098	A1	19980313	FR 1996-10875	19960906
FR 2753098	B1	19981127		
CA 2264901	AA	19980312	CA 1997-2264901	19970905

AU 9742111	A1	19980326	AU 1997-42111		19970905
AU 734296	B2	20010607			
EP 939654	A1	19990908	EP 1997-940183		19970905
EP 939654	B1	20040421			
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI					
NZ 334597	A	20001027	NZ 1997-334597		19970905
JP 2000517336	T2	20001226	JP 1998-512314		19970905
RU 2174844	C2	20011020	RU 1999-106792		19970905
AT 264692	E	20040515	AT 1997-940183		19970905
US 6297281	B1	20011002	US 1999-254254		19990302
NO 9901100	A	19990505	NO 1999-1100		19990305
PRIORITY APPLN. INFO.:			FR 1996-10875	A	19960906
			WO 1997-FR1567	W	19970905

AB The invention concerns a pharmaceutical composition containing, as active principle, at least one NO synthase-inhibiting substance and at least one reactive oxygen-trapping substance, optionally with a pharmaceutically acceptable support. The invention also concerns a product containing at least one NO synthase-inhibiting substance and at least one reactive oxygen-trapping substance as combined product of these active principles in **sep.** form.

IT **79-17-4, Aminoguanidine 306-60-5, Agmatine 616-91-1, N-Acetyl cysteine 2986-20-1, S-Ethylisothiourea 17035-90-4 22780-54-7, 2-Iminopiperidine 156719-41-4, S-Methyl-L-thiocitrulline 158875-72-0, S-Ethyl-L-thiocitrulline**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); PEP (Physical, engineering or chemical process); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(association of NO synthase inhibitors with trappers of reactive oxygen species)

REFERENCE COUNT: 1 THERE ARE 1 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L22 ANSWER 5 OF 8 CAPLUS COPYRIGHT 2004 ACS on STN
ED Entered STN: 08 Feb 1996
ACCESSION NUMBER: 1996:83797 CAPLUS
DOCUMENT NUMBER: 124:194229
TITLE: Effect of selected anti-cataract agents on opacification in the selenite cataract model
AUTHOR(S): Hiraoka, T.; Clark, J. I.; Li, X. Y.; Thurston, G. M.
CORPORATE SOURCE: Dep. Biol. Structure, Univ. Washington, Seattle, WA, 98195, USA
SOURCE: Experimental Eye Research (1996), 62(1), 11-19
CODEN: EXERA6; ISSN: 0014-4835
PUBLISHER: Academic
DOCUMENT TYPE: Journal
LANGUAGE: English

AB A systematic study of the anti-cataract activity of 14 reagents was conducted using the selenite model. The reagents or their derivs. were identified from literature reports of their potential effectiveness against cataract formation. The effects of each reagent were measured on the phase **separation** temperature, Tc, of lens homogenate in vitro. Tc is a

direct measure of mol. interaction leading to protein aggregation. The protective effect of a single s.c. injection of each reagent [at a dose of 1.5 mmol/kg body weight] on lens opacification was evaluated in vivo using rats administered selenite [at a dose of 19 μmol/kg body weight] to initiate cataract formation. The strongest effects on lens opacification in vivo were observed with reagents having the strongest effect on Tc, in vitro. The weakest effects in vivo were observed with the reagents having the weakest effect on Tc, in vitro. The results were suggestive of a relation between the effect of reagent on Tc and protection against cataract formation in vivo.

IT **52-67-5**, D-**Penicillamine 79-17-4**, **Aminoguanidine**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(effect of selected anti-cataract agents on opacification in selenite cataract model)

L22 ANSWER 6 OF 8 CAPLUS COPYRIGHT 2004 ACS on STN
ED Entered STN: 05 Feb 1994
ACCESSION NUMBER: 1994:45589 CAPLUS
DOCUMENT NUMBER: 120:45589
TITLE: Regional and cardiac hemodynamic effects of NG,NG, dimethyl-L-arginine and their reversibility by vasodilators in conscious rats
AUTHOR(S): Gardiner, S. M.; Kemp. P. A.; Bennett, T.; Palmer, R. M. J.; Moncada, S.
CORPORATE SOURCE: Univ. Nottingham Med. Sch., Nottingham, NG7 2UH, UK
SOURCE: British Journal of Pharmacology (1993), 110(4), 1457-64
CODEN: BJPCBM; ISSN: 0007-1188
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Expts. were carried out on 3 **sep**. groups of male Long Evans rats, chronically instrumented for the measurement of regional hemodynamics, to compare the effects of NG,NG,dimethyl-L-arginine (ADMA) and NG-monomethyl-L-arginine (L-NMMA), and their reversibility by the nitric oxide donors, S-nitroso-N-acetyl-**penicillamine** (SNAP), S-nitroso-glutathione (SNOG), Na nitroprusside (SNP), and the vasodilator, hydralazine. As previously reported for L-NMMA, ADMA (1-100 mg kg-1) caused dose-depend pressor and bradycardiac effects, accompanied by renal, mesenteric and hindquarters vasoconstrictions. The magnitude and duration of these effects were similar for ADMA and L-NMMA, consistent with their being equipotent inhibitors of nitric oxide synthase. Infusion of SNAP or SNOG (300 μg kg-1 h-1) after injection of ADMA or L-NMMA (100 mg kg-1) reversed the pressor but did not abolish the vasoconstrictor, effects of ADMA or L-NMMA. However, a higher dose of SNAP (3 mg kg-1 h-1) caused complete reversal of the pressor and mesenteric hemodynamic effects of ADMA (100 mg kg-1), although its renal and hindquarters vasoconstrictor effects were not abolished. Infusion of SNP (300 μg kg-1 h-1) after administration of L-NMMA (100 mg kg-1), caused complete reversal of its pressor and mesenteric and hindquarters hemodynamics effects, and reduced substantially its renal vasoconstrictor action; hydralazine (7.5 mg kg-1 h-1) was almost as effective as SNP in reversing all these variables. In animals chronically instrumented for the measurement of cardiac hemodynamics, ADMA (100 mg kg-1) caused a pressor effect accompanied by a

rise in central venous pressure, and redns. in heart rate, cardiac index, stroke index, peak aortic flow, maximum rate of rise of aortic flow and total peripheral conductance. The reversal of the pressor effect of ADMA by SNAP (300 μg kg-1 h-1) was accompanied by a reduction of central venous pressure below resting levels and a further diminution of stroke index; all other variables showed an increase, but they still remained above resting levels (with the exception of heart rate). Thus, following inhibition of NO formation, pharmacol. intervention with NO donors, or other vasodilators, may cause normalization of the mean arterial pressure without necessarily returning all associated cardiovascular variables to normal.

IT **17035-90-4**, NG-Monomethyl-L-arginine
RL: BIOL (Biological study)
(heart rate decrease and hypertension and vasoconstriction from, vasodilators effect on)

L22 ANSWER 7 OF 8 CAPLUS COPYRIGHT 2004 ACS on STN
ED Entered STN: 01 Nov 1986
ACCESSION NUMBER: 1986:548695 CAPLUS
DOCUMENT NUMBER: 105:148695
TITLE: Amino acid specific ADP-ribosylation: substrate specificity of an ADP-ribosylarginine hydrolase from turkey erythrocytes
AUTHOR(S): Moss, Joel; Oppenheimer, Norman J.; West, Robert E., Jr.; Stanley, Sally J.
CORPORATE SOURCE: Lab. Cell. Metab., Natl. Heart, Lung, Blood Inst., Bethesda, MD, 20892, USA
SOURCE: Biochemistry (1986), 25(19), 5408-14
CODEN: BICHAW; ISSN: 0006-2960
DOCUMENT TYPE: Journal
LANGUAGE: English

AB ADP-ribosylarginine hydrolase (I), which catalyzes the degradation of ADP-ribosyl[14C]arginine to ADP-ribose plus arginine, was **separated** by ion-exchange, hydrophobic, and gel permeation chromatog. from NAD-arginine ADP-ribosyltransferases, which are responsible for the stereospecific formation of α-ADP-ribosylarginine. As determined by NMR, the specific substrate for I was α-ADP-ribosylarginine, the product of the transferase reaction. The ADP-ribose moiety was critical for substrate recognition; (phosphoribosyl)[14C]arginine and ribosyl[14C]arginine were poor substrates and did not significantly inhibit ADP-ribosyl[14C]arginine degradation In contrast, ADP-ribose was a potent inhibitor of I and significantly more active than ADP > AMP > adenosine. In addition to ADP-ribosyl[14C]arginine, both ADP-ribosyl[14C]guanidine and (2'-phospho-ADP-ribosyl)[14C]arginine were also substrates; at pH <7, ADP-ribosyl[14C]guanidine was degraded more readily than the [14C]arginine derivative Neither arginine, guanidine, nor **agmatine**, an arginine analog, was an effective I inhibitor. Apparently, the ADP-ribosyl moiety but not the arginine group is critical for substrate recognition. Although I requires a thiol for activity, **dithiothreitol** accelerated loss of activity during incubation at 37°. Stability was enhanced by Mg2+, which was also necessary for optimal enzymic activity. These findings were consistent with the conclusion that different enzymes catalyze ADP-ribosylarginine synthesis and degradation Furthermore, since I and the transferases possess a

compatible stereospecificity and substrate specificity, the 2 enzymic activities apparently may serve as opposing arms in an ADP-ribosylation cycle.

L22 ANSWER 8 OF 8 CAPLUS COPYRIGHT 2004 ACS on STN
ED Entered STN: 12 May 1984
ACCESSION NUMBER: 1980:71602 CAPLUS
DOCUMENT NUMBER: 92:71602
TITLE: Arginine decarboxylase of oat seedlings
AUTHOR(S): Smith, Terence A.
CORPORATE SOURCE: Res. Stn., Univ. Bristol, Bristol, BS18 9AF, UK
SOURCE: Phytochemistry (Elsevier) (1979), 18(9), 1447-52
CODEN: PYTCAS; ISSN: 0031-9422
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Arginine decarboxylase (EC 4.1.1.19) (I) from the shoots of K deficient oat seedlings was **separated** into 2 fractions; I-A (mol. weight 195,000) had a sp. activity .apprx.6-fold higher than I-B (mol. weight 118,000). The proportion of I-A to I-B in plants supplied with normal K concns. was similar to that in K deficient plants, although the total I activity was 5-fold higher in the latter. The properties of I-A and I-B were similar with respect to pH optimum (7-7.5), Km (3 + 10-5M), and effect of inhibitors. I was specific for L-arginine and was strongly inhibited by NSD 1055, D-arginine, and canavanine. Mercaptoethanol and **dithiothreitol** stimulated I by .apprx.50% and p-chloromercuribenzoate was an inhibitor. Pyridoxal phosphate and EDTA both stimulated activity by .apprx.30%, and Ca and Mg inhibited activity by 50% at .apprx.20 mM. Putrescine and the polyamines showed only moderate inhibition at 10 mM, but **agmatine** reduced activity to 30% at this concentration

(FILE 'MEDLINE, BIOSIS, EMBASE, WPIDS, CONFSCI, SCISEARCH, JICST-EPLUS, JAPIO' ENTERED AT 12:22:26 ON 05 NOV 2004)
L23 36 S L21
L24 35 S L23 NOT L5
L25 27 DUP REM L24 (8 DUPLICATES REMOVED)

L25 ANSWER 1 OF 27 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED. on STN
ACCESSION NUMBER: 2003243875 EMBASE
TITLE: Interplay between high energy impulse noise (blast) and antioxidants in the lung.
AUTHOR: Elsayed N.M.; Gorbunov N.V.
CORPORATE SOURCE: N.M. Elsayed, Hurley Consulting Associates, One Main Street, Chatham, NJ 07928, United States.
nelsayed@hurleyconsulting.com
SOURCE: Toxicology, (15 Jul 2003) 189/1-2 (63-74).
Refs: 66
ISSN: 0300-483X CODEN: TXCYAC
COUNTRY: Ireland
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 005 General Pathology and Pathological Anatomy
011 Otorhinolaryngology
015 Chest Diseases, Thoracic Surgery and Tuberculosis
030 Pharmacology
037 Drug Literature Index

Searcher : Shears 571-272-2528

LANGUAGE: English
SUMMARY LANGUAGE: English

AB High-energy impulse noise (BLAST) is a physical event characterized by an abrupt rise in atmospheric pressure above ambient lasting for a very short period, but potentially causing significant material and biological damage. Exposure to high-level BLAST can be destructive and lethal. Low-level BLAST similar to what is encountered repeatedly by military personnel during training and combat from detonation of munitions and firing of large caliber weapons, and during occupational use of explosives and some heavy machinery, can also cause significant injury. Globally, civilians are increasingly exposed to BLAST resulting from terrorist bombings or abandoned unmarked mines following numerous wars and conflicts. We have shown previously in several animal models that exposure to non-lethal BLAST results in pathological changes, mostly to the hollow organs characterized in the lungs, the most sensitive organ, by rupture of alveolar **septa**, and pulmonary hemorrhage and edema. These events potentially can cause alveolar flooding, respiratory insufficiency and adult respiratory distress syndrome (ARDS), leading to varying degrees of hypoxia, antioxidant depletion and oxidative damage. We have also observed progressive formation of nitric oxide in blood and other tissues. The totality of these observations supports our general hypothesis that exposure to BLAST can lead to antioxidant depletion and oxidative damage. Understanding the mechanism(s) of BLAST-induced oxidative stress may have important implications that include a potential beneficial role for antioxidants as a prophylaxis or as secondary treatment of injury after exposure alongside other protective and therapeutic modalities. In addition, it suggests a role for endogenous nitric oxide in the injury. This report reviews experimental evidence of BLAST-induced antioxidant depletion, and the potential benefit from antioxidant supplementation before exposure. .COPYRGT. 2003 Elsevier Science Ireland Ltd. All rights reserved.

L25 ANSWER 2 OF 27 WPIDS COPYRIGHT 2004 THE THOMSON CORP on STN
ACCESSION NUMBER: 2002-351847 [38] WPIDS
DOC. NO. NON-CPI: N2002-276448
DOC. NO. CPI: C2002-099961
TITLE: Peritoneal dialysate for treating renal failure comprises electrolytic salts, glucose and protein crosslinking inhibitor or protein crosslinkage dissociating agent.
DERWENT CLASS: B04 P34
INVENTOR(S): NAKAYAMA, M; SAKAI, A
PATENT ASSIGNEE(S): (NISC-N) JAPAN SCI & TECHNOLOGY CORP; (KAGA-N) KAGAKU GIJUTSU SHINKO JIGYODAN; (SAKA-I) SAKAI A; (NAKA-I) NAKAYAMA M
COUNTRY COUNT: 25
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
WO 2002022188	A1	20020321	(200238)*	JA	22
RW: AT BE CH CY DE DK ES FI FR GB GR IE IT LU MC NL PT SE TR					
W: CA CN KR US					
JP 2002315825	A	20021029	(200303)		10
EP 1323440	A1	20030702	(200344)	EN	
R: AT BE CH CY DE DK ES FI FR GB GR IE IT LI LU MC NL PT SE TR					
KR 2003040450	A	20030522	(200360)		

CN 1458850 A 20031126 (200413)
US 2004096845 A1 20040520 (200434)

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 2002022188	A1	WO 2001-JP7772	20010907
JP 2002315825	A	JP 2001-186642	20010620
EP 1323440	A1	EP 2001-963506	20010907
		WO 2001-JP7772	20010907
KR 2003040450	A	KR 2003-703487	20030310
CN 1458850	A	CN 2001-815509	20010907
US 2004096845	A1	WO 2001-JP7772	20010907
		US 2003-380350	20030313

FILING DETAILS:

PATENT NO	KIND	PATENT NO
EP 1323440	A1 Based on	WO 2002022188

PRIORITY APPLN. INFO: JP 2001-186642 20010620; JP 2000-277810 20000913; JP 2001-40718 20010216

AN 2002-351847 [38] WPIDS

AB WO 200222188 A UPAB: 20020618

NOVELTY - Peritoneal dialysate (I) comprises electrolytic salts, glucose and a protein crosslinking inhibitor (A) and/or a protein crosslinkage dissociating agent (B).

ACTIVITY - Nephrotropic; Dialysis.

MECHANISM OF ACTION - Antioxidant; Protein crosslinking inhibitor.

In a glycation induced crosslinking model, peritoneal dialysate containing human albumin (50 mg/ml), glucose (20 mM/l) and **N-acetylcysteine** (20 mM/l), showed 7% crosslinking compared to 100% for a control without **N-acetylcysteine** after 2 weeks at 37 deg. C.

USE - For treating renal failure.

ADVANTAGE - Prevents and/or dissociates protein crosslinking due to oxidation and/or denaturation of glucose, preventing hardening of peritoneal tissue and allowing dialysis to continue.

Dwg.0/0

L25 ANSWER 3 OF 27 WPIDS COPYRIGHT 2004 THE THOMSON CORP on STN

ACCESSION NUMBER: 2002-642151 [69] WPIDS

CROSS REFERENCE: 2002-535404 [57]

DOC. NO. CPI: C2004-014029

TITLE: Method of reducing immunosuppressive effects or toxicity of interleukin-12 by co-administering nitric oxide inhibitor and/or neutralizing agent e.g. allylarginine, **7-nitro indazole, aminoguanidine,** diphenyleneiodonium.

DERWENT CLASS: B05

INVENTOR(S): KOBLISH, H; LEE, W M F; TRINCHIERI, G

PATENT ASSIGNEE(S): (KOBL-I) KOBLISH H; (LEEW-I) LEE W M F; (TRIN-I) TRINCHIERI G

COUNTRY COUNT: 1
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
US 2002081277	A1	20020627	(200269)*		19

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
US 2002081277	A1 Provisional	US 1998-101698P	19980925
	Div ex	US 1999-395038	19990913
		US 2002-79068	20020220

FILING DETAILS:

PATENT NO	KIND	PATENT NO
US 2002081277	A1 Div ex	US 6375944

PRIORITY APPLN. INFO: US 1998-101698P 19980925; US 1999-395038 19990913; US 2002-79068 20020220

AN 2002-642151 [69] WPIDS
CR 2002-535404 [57]
AB US2002081277 A UPAB: 20040408
NOVELTY - Method for reducing the immunosuppressive effects or toxicity of interleukin-12 (IL-12) comprises co-administering a nitric oxide (NO) inhibiting and/or neutralizing agent.

DETAILED DESCRIPTION - Method for reducing the immunosuppressive effects of IL-12 treatment comprises co-administering with the IL-12, a NO inhibiting and/or neutralizing agent.

INDEPENDENT CLAIMS are also included for:

(1) Method for reducing the toxicity of IL-12 treatment comprising co-administering with the IL-12, a NO inhibiting and reducing agent;

(2) Therapeutic composition comprising IL-12 characterized by reduced toxicity in mammals, the composition comprising a dose of IL-12 and a NO inhibiting and/or neutralizing agent in a carrier.

ACTIVITY - Immunostimulant; Cytostatic; Virucide; Antiparasitic; Protozoacide; Anthelminthic; Anti-HIV; Tuberculostatic; Antileprotic.

MECHANISM OF ACTION - Inhibitors of NO.

USE - IL-12 is an immunoregulatory cytokine with potent antitumor, antiparasitic, antiviral and antimicrobial effects. The methods can be used for reducing the immunosuppressive effects or toxicity of IL-12 treatment. The IL-12 can be used as an adjuvant for a vaccine composition containing an antigen such as a cancer antigen or an antigen from a pathogen e.g. bacteria, protozoa, helminths, viruses and parasites which are the causative agents of diseases such as HIV, Hepatitis A, Hepatitis B, Hepatitis C, rabies virus, poliovirus, influenza virus, meningitis virus, measles virus, mumps virus, rubella, pertussis, encephalitis virus, papilloma virus, yellow fever virus, respiratory syncytial virus, parvovirus, chikungunya virus, hemorrhagic fever viruses, Klebsiella, and Herpes viruses, particularly, varicella, cytomegalovirus and Epstein-Barr virus, leprosy and tuberculosis, leishmaniasis and malaria or schistosomiasis.

Searcher : Shears 571-272-2528

ADVANTAGE - The methods can reduce or eliminate the suppression of cellular immune response caused by administration of IL-12. The method enables the use of the low doses of IL-12 in therapy, which will reduce the toxic side effects noted with the currently used high doses (100-1000 ng/kg).

Female A/J mice were vaccinated with 106 irradiated SCK.GM cells suspended in PBS at 107 trypan blue-excluding cells/ml. Cells were irradiated with 6000 rads from a 137Cs source, and mice were vaccinated with 106 cells s.c. (day 0). Mice were given either rmIL-12 injected intraperitoneally (ip) 250ng/day on days 0-4 and 7-11 (10 injections), or rmIL-12+ L-NAME (an inhibitor of iNOS that acts similarly to L-NMMA), or rmIL-12 and D-NAME (the inactive isoform) injected at the same dosage and regimen, while control mice received PBS injections. Vaccinated and naive A/J mice were challenged 14 days after vaccination with 2.5x104 trypan blue-excluding SCK cells in the opposite flank to assay for the presence of tumor immunity. Tumorigenesis was scored daily. The results showed the difference in tumorigenesis between rmIL-12 treated mice given L-NAME vs. either D-NAME or nothing is statistically significant at p at most 0.05. Data was compiled from 2 **separate** experiments that produced consistent results (15-17 mice per group total). As expected, SCK.GM vaccination protected the great majority of mice from tumor cell challenge two weeks after vaccination, and rmIL-12 severely impaired this protection. L-NAME but not D-NAME prevented this impairment (75% developed tumors). In mice not treated with rmIL-12, L-NAME and D-NAME had no effect on SCK. GM-induced protection showing that L-NAME acts by preventing rmIL-12 suppression of SCK.GM vaccine efficacy. Further studies showed that rmIL-12 improved SCK cell vaccine efficacy markedly and rapidly, but that the improvement at day 14 was obscured by rmIL-12 immunosuppressive effect.

Dwg.0/7

L25 ANSWER 4 OF 27 MEDLINE on STN DUPLICATE 1

ACCESSION NUMBER: 2002690650 MEDLINE
DOCUMENT NUMBER: PubMed ID: 12438523
TITLE: Role of spinal nitric oxide in the inhibitory effect of [D-Pen2, D-Pen5]-enkephalin on ascending dorsal horn neurons in normal and diabetic rats.
AUTHOR: Khan Ghous M; Li De-Pei; Chen Shao-Rui; Pan Hui-Lin
CORPORATE SOURCE: Department of Anesthesiology, Penn State University College of Medicine, Hershey, Pennsylvania 17033, USA.
CONTRACT NUMBER: GM64830 (NIGMS)
NS41178 (NINDS)
SOURCE: Journal of pharmacology and experimental therapeutics, (2002 Dec) 303 (3) 1021-8.
Journal code: 0376362. ISSN: 0022-3565.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200212
ENTRY DATE: Entered STN: 20021214
Last Updated on STN: 20021227
Entered Medline: 20021224

AB Intrathecal [D-Pen2,D-Pen5]-enkephalin (DPDPE; a delta-opioid agonist) has a profound antinociceptive effect in neuropathic pain. Spinal nitric oxide (NO) has been implicated in the analgesic effect of several G

protein-coupled receptor agonists. Little, however, is known about the role of spinal NO in the inhibitory effect of DPDPE on spinal dorsal horn neurons. In the present study, we determined the role of NO in the inhibitory effect of DPDPE on ascending dorsal horn neurons in normal rats and in a rat model of diabetic neuropathic pain. Single-unit activity of ascending dorsal horn neurons was recorded in anesthetized rats. The responses of dorsal horn neurons to graded mechanical stimuli and von Frey filaments were determined before and after local spinal application of 0.1 to 5 microM DPDPE. The influence of an NO synthase inhibitor, **1-(2-trifluoromethylphenyl)** imidazole (TRIM; 30 microM), on the effect of DPDPE was then studied in **separate** groups of dorsal horn neurons in normal and diabetic rats. DPDPE inhibited the response of dorsal horn neurons in both normal and diabetic rats in a concentration-dependent fashion. The inhibitory effect of 1 microM DPDPE was abolished by 1 microM naltrindole, a delta-opioid antagonist. Furthermore, the inhibitory effect of DPDPE on the evoked response of dorsal horn neurons was largely eliminated by TRIM in normal and diabetic rats. These data suggest that DPDPE has a profound inhibitory effect on dorsal horn neurons in normal and diabetic rats. Spinal endogenous NO is essential for the inhibitory effect of DPDPE on ascending dorsal horn neurons in both normal and diabetic rats.

L25 ANSWER 5 OF 27 EMBASE
on STN

ACCESSION NUMBER: 2002422000 EMBASE
TITLE: Physiological concentrations of insulin induce endothelin-mediated vasoconstriction during inhibition of NOS or PI3-kinase in skeletal muscle arterioles.
AUTHOR: Eringa E.C.; Stehouwer C.D.A.; Merlijn T.; Westerhof N.; Sipkema P.
CORPORATE SOURCE: P. Sipkema, Laboratory for Physiology, VU Medical Centre, van der Boechorststraat 7, 1081 BT Amsterdam, Netherlands. sipkema@physiol.med.vu.nl
SOURCE: Cardiovascular Research, (1 Dec 2002) 56/3 (464-471). Refs: 39
ISSN: 0008-6363 CODEN: CVREAU
PUBLISHER IDENT.: S 0008-6363(02)00593-X
COUNTRY: Netherlands
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 018 Cardiovascular Diseases and Cardiovascular Surgery
029 Clinical Biochemistry
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English
AB Objective: To determine the roles of nitric oxide, endothelin-1 and phosphatidylinositol 3-kinase (PI3-kinase) in acute responses of isolated rat skeletal muscle arterioles to insulin. Methods: Rat cremaster first order arterioles were **separated** from surrounding tissue, cannulated in a pressure myograph and responses to insulin (4 μU/ml-3.4 mU/ml) were studied without intraluminal blood or flow. Results: Insulin alone did not significantly affect arteriolar diameter. Non-selective antagonism of endothelin receptors, with PD-142893, uncovered insulin-induced vasodilatation (25±8% from baseline at 3.4 mU/ml), which was abolished by inhibition of NO synthesis with N(G)-nitro-L-arginine (L-NA). Inhibition of NO synthesis alone uncovered insulin-induced vasoconstriction at physiological concentrations (21±5%

from baseline diameter at 34 μU/ml), which was abolished by PD-142893. The NO donor, S-nitroso-N-acetyl-**penicillamine** (SNAP) inhibited insulin-induced vasoconstriction during NOS inhibition, even at a concentration that did not elicit vasodilatation itself. Inhibition of PI3-kinase, an intracellular mediator of insulin-induced NO production, with wortmannin, also uncovered insulin-induced vasoconstriction (13±3% from baseline at 34 μU/ml) that was abolished by PD-142893. Conclusions: Insulin induces both nitric oxide and endothelin-1 activity in rat cremaster first-order arterioles. This study demonstrates for the first time that vasoconstrictive effects of physiological concentrations of insulin during inhibition of NOS activity are mediated by endothelin and that insulin induces endothelin-1-mediated vasoconstriction in isolated skeletal muscle arterioles during inhibition of PI3-kinase. These findings support the hypothesis of altered microvascular reactivity to insulin in conditions of diminished PI3-kinase activity, a prominent feature of insulin resistance. .COPYRGT. 2002 Elsevier Science B.V. All rights reserved.

L25 ANSWER 6 OF 27 WPIDS COPYRIGHT 2004 THE THOMSON CORP on STN
ACCESSION NUMBER: 2002-034382 [04] WPIDS
DOC. NO. NON-CPI: N2002-026480
DOC. NO. CPI: C2002-009610
TITLE: Identifying compounds which regulates glycation of protein, such as carbonyl scavengers which affect cellular stress, by combining the compound with histone H1 and ADP-ribose and measuring fluorescence.
DERWENT CLASS: B04 D16 S03
INVENTOR(S): JACOBSON, E L; JACOBSON, M K; WONDRAK, G T
PATENT ASSIGNEE(S): (NIAD-N) NIADYNE CORP; (KENT) UNIV KENTUCKY; (JACO-I) JACOBSON E L; (JACO-I) JACOBSON M K; (WOND-I) WONDRAK G T; (KENT) UNIV KENTUCKY RES FOUND
COUNTRY COUNT: 92
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
WO 2001079842	A2	20011025	(200204)*	EN	40
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ NL OA PT SD SE SL SZ TR TZ UG ZW					
W: AE AL AM AT AU AZ BA BB BG BR BY CA CH CN CR CU CZ DE DK DM EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT TZ UA UG US UZ VN YU ZA ZW					
AU 2001053555	A	20011030	(200219)		
US 2002037496	A1	20020328	(200225)		
EP 1272843	A2	20030108	(200311)	EN	
R: AL AT BE CH CY DE DK ES FI FR GB GR IE IT LI LT LU LV MC MK NL PT RO SE SI TR					
JP 2003531376	W	20031021	(200373)		44
CN 1451096	A	20031022	(200406)		
US 6716635	B2	20040406	(200425)		

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE

WO 2001079842	A2	WO 2001-US12368	20010416
AU 2001053555	A	AU 2001-53555	20010416
US 2002037496	A1 Provisional	US 2000-197829P	20000414
		US 2001-836576	20010416
EP 1272843	A2	EP 2001-927070	20010416
		WO 2001-US12368	20010416
JP 2003531376	W	JP 2001-576457	20010416
		WO 2001-US12368	20010416
CN 1451096	A	CN 2001-810726	20010416
US 6716635	B2 Provisional	US 2000-197829P	20000414
		US 2001-836576	20010416

FILING DETAILS:

PATENT NO	KIND	PATENT NO
AU 2001053555	A Based on	WO 2001079842
EP 1272843	A2 Based on	WO 2001079842
JP 2003531376	W Based on	WO 2001079842

PRIORITY APPLN. INFO: US 2000-197829P 20000414; US 2001-836576 20010416

AN 2002-034382 [04] WPIDS

AB WO 200179842 A UPAB: 20020117

NOVELTY - Determining a substance which regulates glycation of a protein, comprises admixing a substance to be tested, a histone H1, and ADP-ribose, and determining whether the substance to be tested has an effect on glycation of histone H1 by ADP-ribose, where indication of an effect on glycation indicates that the substance regulates glycation.

DETAILED DESCRIPTION - An INDEPENDENT CLAIM is also included for a kit useful in determining if a substance is capable of regulating protein glycation, comprising a container and **separate** portions of each of histone H1 and ADP-ribose.

ACTIVITY - Antidiabetic; Antiatherosclerotic; Neuroprotective; Nootropic.

No supporting data is given.

MECHANISM OF ACTION - Inhibitor of protein-AGE formation.

USE - The method is useful for identifying a substance such as dicarbonyl scavenger, nucleophilic thiol containing compound and not an antioxidant which regulates glycation of a protein (claimed). The identified compounds affect cellular stress and inhibit protein-AGE formation. The method is useful in determining substances of interest in impacting pathological conditions with which protein-AGE formation is associated, such as diabetes, atherosclerosis, chronic neurodegenerative diseases, such as Alzheimer's disease, skin photoaging and other degenerative diseases characteristics of the aging process.

DESCRIPTION OF DRAWING(S) - Figure depicts results of an experiment designed to determine the protective effect of D-**penicillamine** on cells which can inhibit the cytotoxic effect of compounds that affect glycation.

Dwg.18/19

L25 ANSWER 7 OF 27 MEDLINE on STN DUPLICATE 2

ACCESSION NUMBER: 2002028685 MEDLINE

DOCUMENT NUMBER: PubMed ID: 11725202

TITLE: Metastatic melanoma cells escape from immunosurveillance

through the novel mechanism of releasing nitric oxide to induce dysfunction of immunocytes.

AUTHOR: Zhang X M; Xu Q
CORPORATE SOURCE: State Key Laboratory of Pharmaceutical Biotechnology, School of Life Sciences, Nanjing University, Nanjing 210093, The People's Republic of China.

SOURCE: Melanoma research, (2001 Dec) 11 (6) 559-67.
Journal code: 9109623. ISSN: 0960-8931.
PUB. COUNTRY: England: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200201
ENTRY DATE: Entered STN: 20020123
Last Updated on STN: 20020201
Entered Medline: 20020131

AB Nitric oxide (NO) is known to facilitate tumour metastasis through the promotion of angiogenesis, vascular dilation, platelet aggregation, etc. In the present study we explored its novel role in producing dysfunction of the host immune system in the metastasis of murine metastatic melanoma B16-BL6 cells. A significant reduction in the mixed lymphocyte reaction (MLR) was observed in the spleen cells from B16-BL6-bearing mice, but not in those from mice bearing the parent cell B16. When B16-BL6 cells were added in vitro to the MLR, a significant decrease was also found, even when they were co-cultured with the lymphocytes in two compartments of a Transwell chamber **separated** by an 8.0 microm filter. The supernatant from cultured B16-BL6 but not B16 cells, which had a greatly increased NO activity, significantly inhibited concanavalin A- and lipopolysaccharide-induced lymphocyte proliferation. A remarkably higher expression of inducible NO synthase (iNOS) was detected in B16-BL6 cells than in B16 cells. Nomega-Nitro-l-arginine (l-NNA), a NO synthase inhibitor and superoxide dismutase, significantly antagonized the above inhibition by B16-BL6 cells, while l-arginine, a NO precursor, and S-nitroso-N-acetyl-d,l-**penicillamine**, a NO donor, strengthened the inhibition. Furthermore, l-NNA significantly inhibited lung metastasis of B16-BL6 cells, while l-arginine tended to enhance the metastasis. The cytotoxicity of B16-BL6-specific T-cells was significantly decreased by pre-culture with B16-BL6 cells in a Transwell chamber or the culture supernatants of B16-BL6 cells, whereas l-iminoethyl-lysine, a selective inhibitor of iNOS, showed a significant recovery from the disease. These results suggest that NO released by metastatic tumour cells may impair the immune system, which facilitates the escape from immunosurveillance and metastasis of tumour cells.

L25 ANSWER 8 OF 27 MEDLINE on STN
ACCESSION NUMBER: 2001695884 MEDLINE
DOCUMENT NUMBER: PubMed ID: 11747143
TITLE: Corpus cavernosum dysfunction in diabetic rats: effects of combined alpha-**lipoic** acid and gamma-linolenic acid treatment.

AUTHOR: Keegan A; Cotter M A; Cameron N E
CORPORATE SOURCE: Department of Biomedical Sciences, University of Aberdeen, Aberdeen, Scotland, UK.

SOURCE: Diabetes/metabolism research and reviews, (2001 Sep-Oct) 17 (5) 380-6.
Journal code: 100883450. ISSN: 1520-7552.

PUB. COUNTRY: England: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200201
ENTRY DATE: Entered STN: 20011218
Last Updated on STN: 20020201
Entered Medline: 20020131

AB BACKGROUND: The effects of streptozotocin-induced diabetes on nitric oxide (NO)-mediated relaxation of rat corpus cavernosum smooth muscle to neurogenic and endothelial stimulation was examined. The aim was to assess the effects of treatment with low doses of the antioxidant, alpha-**lipoic** acid, and the omega-6 essential fatty acid, gamma-linolenic acid, either **separately** or in combination. METHODS: Treatment was preventive from diabetes induction or corrective over 4 weeks after 4 weeks of untreated diabetes. Corpus cavernosum responses were examined in vitro. RESULTS: Neither diabetes nor treatment affected contractile responses to transmural electrical field stimulation of noradrenergic nerves. Stimulation of phenylephrine precontracted cavernosa in the presence of guanethidine and atropine caused relaxation via the nitrergic innervation. Maximum relaxation responses were 40% and 46% decreased after 4 and 8 weeks of diabetes, respectively. alpha-**Lipoic** acid, gamma-linolenic acid combination treatment fully prevented this deficit, and partially (52%) corrected the effect of 4 weeks of untreated diabetes. Neither alpha-**lipoic** acid nor gamma-linolenic components alone had significant effects, which suggests that there were synergistic interactions between the drugs. Both 4 and 8 weeks of untreated diabetes reduced maximum endothelium-dependent relaxation of phenylephrine precontracted cavernosa to acetylcholine by approximately 40%. While alpha-**lipoic** acid or gamma-linolenic acid were ineffective, joint treatment fully prevented and corrected this diabetic endothelial deficit. Neither diabetes nor treatment affected endothelium-independent relaxation to the NO donor, sodium nitroprusside. CONCLUSION: The data show that alpha-**lipoic** acid and gamma-linolenic acid interact synergistically to improve NO-mediated neurogenic and endothelium-dependent relaxation of corpus cavernosum in experimental diabetes.

L25 ANSWER 9 OF 27 MEDLINE on STN
ACCESSION NUMBER: 2002188548 MEDLINE
DOCUMENT NUMBER: PubMed ID: 11852423
TITLE: Dual action of nitric oxide on purely isolated retinal ganglion cells.
AUTHOR: Kashiwagi K; Iizuka Y; Tanaka Y; Mochizuki S; Kajiya F; Araie M; Suzuki Y; Iijima H; Tsukahara S
CORPORATE SOURCE: Department of Ophthalmology, Yamanashi Medical University, Tamaho Yamanashi, Japan.. kenjik@res.yamanashi-med.ac.jp
SOURCE: Current eye research, (2001 Oct) 23 (4) 233-9.
Journal code: 8104312. ISSN: 0271-3683.
PUB. COUNTRY: England: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200204
ENTRY DATE: Entered STN: 20020403

Searcher : Shears 571-272-2528

Last Updated on STN: 20020423
Entered Medline: 20020422

AB PURPOSE: The role of nitric oxide (NO) in the survival of retinal ganglion cells (RGCs) was investigated. METHODS: RGCs were purely isolated from postnatal Sprague-Dawley rats by 2-step panning and were cultured in chemically defined serum free medium. An NO releaser, S-nitroso-N-acetylpenicillamine (SNAP: 500 microM, 250 microM, 100 microM, 10 microM, 1 microM, 100 nM, and 10 nM), an NO scavenger, 2-(4-carboxyphenyl)-4,4,5,5 tetramethylimidazoline-1-oxyl-3-oxide potassium salt (c-PTIO: 100 microM, 33 microM, 10 microM, 1 microM), mixture of 100 microM SNAP and 33 microM c-PTIO, N(G)-nitro-L-arginine methyl ester (L-NAME: 10 mM, 5 mM, 500 microM, 100 microM or 10 microM), or their vehicles were added to the medium of pure RGC culture for 48 hr. Survival rates of small and large RGCs were determined **separately** by flow cytometry. RESULTS: At > or = 100 microM, SNAP significantly reduced RGC survival in a concentration dependent manner. At < or = 41 microM, SNAP significantly increased survival, particularly of large RGCs. c-PTIO and L-NAME reduced the survival rates concentration-dependently. A mixture of 100 microM SNAP and 33 microM c-PTIO significantly improved RGC survival compared with when they were added on their own. CONCLUSIONS: These results indicate that NO exhibits neuroprotective and neurotoxic actions on RGCs and that low concentrations of NO may be beneficial for the survival of neonatal RGCs in vitro.

L25 ANSWER 10 OF 27 MEDLINE on STN DUPLICATE 3
ACCESSION NUMBER: 2001682995 MEDLINE
DOCUMENT NUMBER: PubMed ID: 11729360
TITLE: Increased nitric oxide accounts for decreased basal vascular tone and responsiveness in the resistance vessels of high-cholesterol-fed rabbits.
AUTHOR: Fitch R; Da Cunha V; Kauser K; Dole W; Parkinson J; Vergona R; Sullivan M E; Wang Y X
CORPORATE SOURCE: Department of Pharmacology, Berlex Biosciences, Richmond, CA 94804-0099, USA.
SOURCE: Pharmacology, (2001) 63 (4) 220-7.
Journal code: 0152016. ISSN: 0031-7012.
PUB. COUNTRY: Switzerland
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200201
ENTRY DATE: Entered STN: 20011203
Last Updated on STN: 20020125
Entered Medline: 20020108

AB The objective of this study was to determine the effects of hypercholesterolemia on basal vascular tone and vascular responses to pharmacologic agents in hindquarter resistance vessels. Blood pressure and hindquarter blood flow were measured in conscious rabbits fed a high cholesterol diet (1%) for 17 weeks (HC) compared to age-matched rabbits fed a normal diet (control). Basal hindquarter blood flow and vascular conductance were significantly higher in HC than in control rabbits. Administration of a non-selective nitric oxide synthase (NOS) inhibitor, L-NAME (100 mg/kg) decreased basal hindquarter blood flow and vascular conductance in a greater magnitude in HC than in control rabbits, thus, abolished the differences in both the flow and conductance between 2 groups, indicating that increased NO was responsible for reduced basal

vascular tone in the HC rabbits. L-NIL (30 mg/kg), a selective inducible NOS (iNOS) inhibitor had no effects on either flow or conductance. This result does not support the involvement of iNOS. In **separate** experiments, animals were anesthetized and instrumented with an extracorporeal circuit to measure perfusion pressure under constant blood flow to the hindquarter vascular bed. In the HC group, vascular responses to acetylcholine, S-nitroso-N-acetyl-**penicillamine** and phenylephrine were all attenuated when compared to the responses in the control rabbits. These results indicate that local overproduction of NO due to hypercholesteremia could desensitize smooth muscle reactivity, thus causing general vascular hyporesponsiveness to vasoactive agents.

L25 ANSWER 11 OF 27 EMBASE
on STN

ACCESSION NUMBER: 2000290794 EMBASE
TITLE: Preventing endotoxin-stimulated alveolar macrophages from decreasing epithelium Na+ channel (ENaC) mRNA levels and activity.
AUTHOR: Dickie A.J.; Rafii B.; Piovesan J.; Davreux C.; Ding J.; Tanswell A.K.; Rotstein O.; O'Brodovich H.
CORPORATE SOURCE: Dr. H. O'Brodovich, Department of Pediatrics, University of Toronto, Hospital for Sick Children, 555 University Avenue, Toronto, Ont. M5G 1X8, Canada
SOURCE: Pediatric Research, (2000) 48/3 (304-310).
Refs: 28
ISSN: 0031-3998 CODEN: PEREBL
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 005 General Pathology and Pathological Anatomy
007 Pediatrics and Pediatric Surgery
LANGUAGE: English
SUMMARY LANGUAGE: English
AB The acute respiratory distress syndrome is characterized by impairment of the alveolar-capillary barrier. Our laboratory has shown that distal lung epithelial cell (DLEC) amiloride-sensitive Na+ transport is impaired by in vitro coculture with endotoxin (lipopolysaccharide)-stimulated alveolar macrophages (AM) through an L-arginine-dependent mechanism. To investigate the effect of this model on mRNA levels of the rat epithelial Na+ channel, mature fetal rat DLEC monolayers were incubated for 16 h with rat AM (1 x 107) and lipopolysaccharide (10 μg/mL), or the cell-free supernatant of lipopolysaccharide-stimulated rat AM. Such exposure resulted in a profound decrease in mRNA expression for all subunits (α, β, and γ) of the rat epithelial Na+ channel, without affecting 18S RNA levels. This effect was prevented by the antioxidant **N-acetylcysteine**. In **separate** experiments, confluent DLEC monolayers were exposed to lipopolysaccharide-stimulated AM supernatant for 16 h with or without **N-acetylcysteine** and DTT and studied in Ussing chambers. As previously demonstrated in our laboratory, AM supernatant resulted m a significant ($p < 0.05$) impairment of DLEC Na+ transport, as reflected by a decrease m the amiloride-sensitive component of short-circuit current (control, 3.96 ± 0.18 μA/cm2 versus supematant, 2.34 ± 0.56 μA/cm2; $p < 0.05$). This effect was significantly reversed by **N-acetylcysteine** (3.55 ± 0.48 μA/cm2), but not by DTT (1.87 ± 0.21 μA/cm2). **N-acetylcysteine**, but not DTT, increased DLEC thiol levels. These

studies elucidate mechanisms by which activated AM impair alveolar epithelial barrier function in an in vitro model of acute lung injury.

L25 ANSWER 12 OF 27 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED. on STN

ACCESSION NUMBER: 2000168217 EMBASE
TITLE: Effects of nitric oxide donors on the afferent resting activity in the cephalopod statocyst.
AUTHOR: Tu Y.; Budelmann B.U.
CORPORATE SOURCE: B.U. Budelmann, Marine Biomedical Institute, University of Texas Medical Branch, 301 University Boulevard, Galveston, TX 77555-1163, United States. bubudelm@utmb.edu
SOURCE: Brain Research, (26 May 2000) 865/2 (211-220).
Refs: 73
ISSN: 0006-8993 CODEN: BRREAP
PUBLISHER IDENT.: S 0006-8993(00)02222-8
COUNTRY: Netherlands
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 002 Physiology
030 Pharmacology
037 Drug Literature Index
008 Neurology and Neurosurgery
LANGUAGE: English
SUMMARY LANGUAGE: English

AB The effects of bath applications of the nitric oxide (NO) donors sodium nitroprusside (SNP), diethylamine sodium (DEA), 3-morpholinosydnonimine (SIN-1), and S-nitroso-N-acetyl-**penicillamine** (SNAP) on the resting activity (RA) of afferent crista fibers were studied in isolated statocysts of the cuttlefish **Sepia** officinalis. The NO donors had three different effects: inhibition, excitation, and excitation followed by an inhibition. The SNAP analog N-acetyl-DL-**penicillamine** (xSNAP; with no NO moiety) had no effect. When the preparation was pre-treated with the NO synthase inhibitor N(G)-nitric-L-arginine methyl ester HCl (L-NAME), the NO donors were still effective. When the preparation was pre-treated with the guanylate cyclase inhibitors methylene blue (M-BLU) or cystamine (CYS), NO donors had only excitatory effects, whereas their effects were inhibitory only when pre-treatment was with the adenylate cyclase inhibitors nicotinic acid (NIC-A), 2',3'-dideoxyadenosine (DDA), or MDL-12330A. When pre-treatment was with a guanylate and an adenylate cyclase inhibitor combined, NO donors had no effect; in that situation, the RA of the afferent fibers remained and the preparation still responded to bath applications of GABA. Selective experiments with statocysts from the squid Sepioteuthis lessoniana and the octopod Octopus vulgaris gave comparable results. These data indicate that in cephalopod statocysts an inhibitory NO-cGMP and an excitatory NO-cAMP signal transduction pathway exist, that these two pathways are the key pathways for the action of NO, and that they have only modulatory effects on, and are not essential for the generation of, the RA. Themes: Neurotransmitters, modulators, transporters, and receptors. Topics: Transmitters in invertebrates. Copyright (C) 2000 Elsevier Science B.V.

L25 ANSWER 13 OF 27 MEDLINE on STN

ACCESSION NUMBER: 2000102861 MEDLINE
DOCUMENT NUMBER: PubMed ID: 10634798
TITLE: Shear-induced increase in hydraulic conductivity in

endothelial cells is mediated by a nitric oxide-dependent mechanism.

AUTHOR: Chang Y S; Yaccino J A; Lakshminarayanan S; Frangos J A; Tarbell J M

CORPORATE SOURCE: Departments of Physiology, Biomolecular Transport Dynamics Laboratory, The Pennsylvania State University, University Park, PA 16802, USA.

CONTRACT NUMBER: HL35549 (NHLBI)
HL57093 (NHLBI)
T32GM08619-01 (NIGMS)

SOURCE: Arteriosclerosis, thrombosis, and vascular biology, (2000 Jan) 20 (1) 35-42.
Journal code: 9505803. ISSN: 1079-5642.

PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals; Space Life Sciences
ENTRY MONTH: 200001
ENTRY DATE: Entered STN: 20000209
Last Updated on STN: 20020121
Entered Medline: 20000128

AB This study addresses the role of nitric oxide (NO) and its downstream mechanism in mediating the shear-induced increase in hydraulic conductivity (L(p)) of bovine aortic endothelial cell monolayers grown on porous polycarbonate filters. Direct exposure of endothelial monolayers to 20-dyne/cm(2) shear stress induced a 4. 70+/-0.20-fold increase in L(p) at the end of 3 hours. Shear stress (20 dyne/cm(2)) also elicited a multiphasic NO production pattern in which a rapid initial production was followed by a less rapid, sustained production. In the absence of shear stress, an exogenous NO donor, S-nitroso-N-acetylpenicillamine, increased endothelial L(p) 2.23+/-0.14-fold (100 micromol/L) and 4.8+/-0.66-fold (500 micromol/L) at the end of 3 hours. In **separate** experiments, bovine aortic endothelial cells exposed to NO synthase inhibitors, N(G)-monomethyl-L-arginine and N(G)-nitro-L-arginine methyl ester, exhibited significant attenuation of shear-induced increase in L(p) in a dose-dependent manner. Inhibition of guanylate cyclase (GC) with LY-83,583 (1 micromol/L) or protein kinase G (PKG) with KT5823 (1 micromol/L) failed to attenuate the shear-induced increase in L(p). Furthermore, direct addition of a stable cGMP analogue, 8-bromo-cGMP, had no effect in altering baseline L(p), indicating that the GC/cGMP/PKG pathway is not involved in shear stress-NO-L(p) response. Incubation with iodoacetate (IAA), a putative inhibitor of glycolysis, dose-dependently increased L(p). Addition of IAA at levels that did not affect baseline L(p) greatly potentiated the response of L(p) to 20-dyne/cm(2) shear stress. Finally, both shear stress-induced and IAA-induced increases in L(p) could be reversed with the addition of dibutyryl cAMP. However, additional metabolic inhibitors, 2 deoxyglucose (10 mmol/L) and oligomycin (1 micromol/L), or reactive oxygen species scavengers, deferoxamine (1 mmol/L) and ascorbate (10 mmol/L), failed to alter shear-induced increases in L(p). Our results show that neither the NO/cGMP/PKG pathway nor a metabolic pathway mediates the shear stress-L(p) response. An alternate mechanism downstream from NO that is sensitive to IAA must mediate this response.

ACCESSION NUMBER: 1999426390 EMBASE
TITLE: Essential thiol requirement to restore pterin- or substrate-binding capability and to regenerate native enzyme-type high-spin heme spectra in the Escherichia coli-expressed tetrahydrobiopterin-free oxygenase domain of neuronal nitric oxide synthase.
AUTHOR: Sono M.; Ledbetter A.P.; McMillan K.; Roman L.J.; Shea T.M.; Masters B.S.S.; Dawson J.H.
CORPORATE SOURCE: M. Sono, Dept. of Chemistry and Biochemistry, University of South Carolina, Columbia, SC 29208, United States. msono@psc.sc.edu
SOURCE: Biochemistry, (30 Nov 1999) 38/48 (15853-15862).
Refs: 61
ISSN: 0006-2960 CODEN: BICHAW
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 029 Clinical Biochemistry
LANGUAGE: English
SUMMARY LANGUAGE: English
AB Nitric oxide (NO) synthases (NOS) are thiolate-ligated heme-, tetrahydrobiopterin (BH4)-, and flavin-containing monooxygenases which catalyze the NADPH-dependent conversion of L-arginine (L-Arg) to NO and citrulline. NOS consists of two domians: an N-terminal oxygenase (heme- and BH4-bound) domain and a C-terminal reductase (FMN- and FAD-bound) domain. In this study, we have spectroscopically examined the binding of L-Arg and BH4 to the dimeric, BH4-free ferric neuronal NOS (nNOS) oxygenase domain expressed in Escherichia coli **separately** from the reductase domain. Addition of L-Arg or its analogue inhibitors (N(G)-methyl-L-Arg, N(G)-nitro-L-Arg) and BH4, together with **dithiothreitol** (DTT), to the pterin-free ferric low-spin oxygenase domain (λ(max): 419,538, 568 nm) and incubation for 2-3 days at 4 °C converted the domain to a native enzyme-type, predominantly high-spin state (λ(max): .apprx.395, .apprx.512, .apprx.650 nm). 7,8-Dihydrobiopterin and other thiols (e.g., β-mercaptoethanol, cysteine, and glutathione, with less effectiveness) can replace BH4 and DTT, respectively. The UV-visible absorption spectrum of L-Arg-bound ferric full-length nNOS, which exhibits a relatively intense band at .apprx.650 nm (ε = 7.5-8 mM-1 cm-1) due to the presence of a neutral flavin semiquinone, can then be quantitatively reconstructed by combining the spectra of equimolar amounts of the oxygenase and reductase domains. Of particular note, the heme spin-state conversion does not occur in the absence of a thiol even after prolonged (35-48 h) incubation of the oxygenase domain with BH4 and/or L-Arg under anaerobic conditions. Thus, DTT (or other thiols) plays a significant role(s) beyond keeping BH4 in its reduced form, in restoring the pterin- and/or substrate- binding capability of the E. coli-expressed, BH4-free, dimeric nNOS oxygenase domain. Our results in combination with recently available X-ray crystallography and site-directed mutagenesis data suggest that the observed DTT effects arise from the involvement of an intersubunit disulfide bond or its rearrangement in the NOS dimer.

L25 ANSWER 15 OF 27 MEDLINE on STN
ACCESSION NUMBER: 2000069597 MEDLINE
DOCUMENT NUMBER: PubMed ID: 10601127
TITLE: Interaction between nitric oxide and endogenous vasoconstrictors in control of renal blood flow.

Searcher : Shears 571-272-2528

AUTHOR: Berthold H; Just A; Kirchheim H R; Ehmke H
CORPORATE SOURCE: I. Physiologisches Institut der Ruprecht-Karls-Universitat Heidelberg, Heidelberg, Germany.
SOURCE: Hypertension, (1999 Dec) 34 (6) 1254-8.
Journal code: 7906255. ISSN: 1524-4563.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200001
ENTRY DATE: Entered STN: 20000131
Last Updated on STN: 20010521
Entered Medline: 20000119

AB The level of renal blood flow (RBF) is controlled by opposing vasoconstrictor and vasodilator influences. In a recent investigation in normotensive dogs, we found that combined blockade of endothelin type A (ET(A)) receptors and angiotensin II formation induces marked increases in RBF that were much larger than the effects of blocking either system alone. The aim of the present study was to determine the contribution of nitric oxide (NO) to this vasodilator response. Experiments were made in 6 conscious, chronically instrumented dogs subjected to 5 different experimental treatments on **separate** days. Blockade of ET(A) receptors alone by the selective antagonist LU 135252 had only minor effects on RBF compared with time-control experiments. Additional blockade of angiotensin II formation by angiotensin-converting enzyme inhibition with trandolaprilat caused a substantial increase of RBF by approximately 50%. This vasodilation was entirely suppressed when NO formation was prevented by inhibition of NO synthase with N(G)-nitro-L-arginine methyl ester HCl. However, when during NO synthase inhibition renal vascular NO concentrations were clamped at control levels by infusing the NO donor S-nitroso-N-acetyl-D, L-**penicillamine**, the vasodilator response to combined blockade of ET(A) receptors and angiotensin II formation was completely restored (DeltaRBF approximately 60%). These results indicate that the vasodilation after combined ET(A) receptor blockade and angiotensin-converting enzyme inhibition is not mediated by an increase in NO release but results from the unmasking of the tonic influence that is normally exerted by constitutively released NO. Accordingly, the tonic activity of endothelial NO synthase appears to be of major importance in the physiological regulation of renal vascular resistance by determining the vasomotor responses to endothelin and angiotensin II.

L25 ANSWER 16 OF 27 MEDLINE on STN
ACCESSION NUMBER: 1999148785 MEDLINE
DOCUMENT NUMBER: PubMed ID: 10025918
TITLE: Inhibition of transforming growth factor beta production by nitric oxide-treated chondrocytes: implications for matrix synthesis.
AUTHOR: Studer R K; Georgescu H I; Miller L A; Evans C H
CORPORATE SOURCE: Ferguson Laboratory for Orthopaedic Research and the University of Pittsburgh School of Medicine, Pennsylvania 15213, USA.
CONTRACT NUMBER: R01-AR-42025 (NIAMS)
SOURCE: Arthritis and rheumatism, (1999 Feb) 42 (2) 248-57.
Journal code: 0370605. ISSN: 0004-3591.
PUB. COUNTRY: United States

DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 199903
ENTRY DATE: Entered STN: 19990316
Last Updated on STN: 19990316
Entered Medline: 19990303

AB OBJECTIVE: Nitric oxide (NO) is generated copiously by articular chondrocytes activated by interleukin-1beta (IL-1beta). If NO production is blocked, much of the IL-1beta inhibition of proteoglycan synthesis is prevented. We tested the hypothesis that this inhibitory effect of NO on proteoglycan synthesis is secondary to changes in chondrocyte transforming growth factor beta (TGFbeta). METHODS: Monolayer, primary cultures of lapine articular chondrocytes and cartilage slices were studied. NO production was determined as nitrite accumulation in the medium. TGFbeta bioactivity in chondrocyte- and cartilage-conditioned medium (CM) was measured with the mink lung epithelial cell bioassay. Proteoglycan synthesis was measured as the incorporation of 35S-sodium sulfate into macromolecules **separated** from unincorporated label by gel filtration on PD-10 columns. RESULTS: IL-1beta increased active TGFbeta in chondrocyte CM by 12 hours; by 24 hours, significant increases in both active and latent TGFbeta were detectable. NG-monomethyl-L-arginine (L-NMA) potentiated the increase in total TGFbeta without affecting the early TGFbeta activation. IL-1beta stimulated a NO-independent, transient increase in TGFbeta3 at 24 hours; however, TGFbeta1 was not changed. When NO synthesis was inhibited with L-NMA, IL-1beta increased CM concentrations of TGFbeta1 from 24-72 hours of culture. L-arginine (10 mM) reversed the inhibitory effect of L-NMA on NO production and blocked the increases in TGFbeta1. Anti-TGFbeta1 antibody prevented the restoration of proteoglycan synthesis by chondrocytes exposed to IL-1beta + L-NMA, confirming that NO inhibition of TGFbeta1 in IL-1beta-treated chondrocytes effected, in part, the decreased proteoglycan synthesis. Furthermore, the increase in TGFbeta and proteoglycan synthesis seen with L-NMA was reversed by the NO donor S-nitroso-N-acetylpenicillamide. Similar results were seen with cartilage slices in organ culture. The autocrine increase in CM TGFbeta1 levels following prior exposure to TGFbeta1 was also blocked by NO. CONCLUSION: NO can modulate proteoglycan synthesis indirectly by decreasing the production of TGFbeta1 by chondrocytes exposed to IL-1beta. It prevents autocrine-stimulated increases in TGFbeta1, thus potentially diminishing the anabolic effects of this cytokine in chondrocytes.

L25 ANSWER 17 OF 27 MEDLINE on STN
ACCESSION NUMBER: 1999194568 MEDLINE
DOCUMENT NUMBER: PubMed ID: 10092524
TITLE: Rapid induction of NF-kappaB binding during liver cell isolation and culture: inhibition by L-NAME indicates a role for nitric oxide synthase.
AUTHOR: Rodriguez-Ariza A; Paine A J
CORPORATE SOURCE: Division of Pharmacology, School of Medicine and Dentistry, Queen Mary & Westfield College, Charterhouse Square, London, EC1M 6BQ, United Kingdom.
SOURCE: Biochemical and biophysical research communications, (1999 Apr 2) 257 (1) 145-8.
Journal code: 0372516. ISSN: 0006-291X.
PUB. COUNTRY: United States

DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199905
ENTRY DATE: Entered STN: 19990525
Last Updated on STN: 19990525
Entered Medline: 19990511

AB This study is the first to demonstrate activation of NF-kappaB binding just 10 minutes into the commonly employed hepatocyte isolation procedure. It is further reported that the anti-oxidant Trolox can prevent the induction of NF-kappaB during the well established hepatocyte isolation procedure but not during their subsequent culture. However both phases of NF-kappaB activation are inhibited by L-NAME intimating a role for NO production, via nitric oxide synthase. These findings demonstrate that at least 2 different signal transduction pathways are operative during hepatocyte isolation and culture. Thus further studies employing Trolox and L-NAME will help delineate how each pathway contributes to the generalised loss of liver function commonly observed in vitro.

L25 ANSWER 18 OF 27 EMBASE
on STN
ACCESSION NUMBER: 1998325214 EMBASE
TITLE: Hypoxic cell death in human NT2-N neurons: Involvement of NMDA and non- NMDA glutamate receptors.
AUTHOR: Rootwelt T.; Dunn M.; Yudkoff M.; Itoh T.; Almaas R.; Pleasure D.
CORPORATE SOURCE: Dr. T. Rootwelt, Department of Pediatric Research, National Hospital, University of Oslo, N-0027 Oslo, Norway
SOURCE: Journal of Neurochemistry, (1998) 71/4 (1544-1553).
Refs: 40
ISSN: 0022-3042 CODEN: JONRA
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 005 General Pathology and Pathological Anatomy
008 Neurology and Neurosurgery
LANGUAGE: English
SUMMARY LANGUAGE: English

AB Human NTera2 teratocarcinoma cells were differentiated into postmitotic NT2-N neurons and exposed to hypoxia for 6 h. The cultures were evaluated microscopically, and percent lactate dehydrogenase (LDH) release after 24 and 48 h was used as an assay for cell death. After 48 h LDH release was 24.3 ± 5.6% versus 13.8 ± 3.7% in controls ($p < 0.001$). Cell death was greatly diminished by MK-801 pretreatment (15.4 ± 5.1%, $p < 0.001$). If glutamine was omitted from the medium, glutamate levels after 6 h of hypoxia were reduced from 101 ± 63 to 2.3 ± 0.3 μM, and cell death at 48 h was also markedly reduced (15.4 ± 4.5%, $p < 0.001$). The α-amino-3-hydroxy-5-methylisoxazole- 4-propionate antagonist 6-cyano-7-nitroquinoxaline-2,3-dione (18.7 ± 5.1%, $p < 0.001$)and mild hypothermia (33.5-34°C) during hypoxia (19.5 ± 2.7%, $p < 0.05$) were moderately protective. Basic fibroblast growth factor (24.1 ± 3.2%), the nitric oxide synthase inhibitor N(G)-nitro-L-arginine methyl ester (22.8 ± 8.1%), the antioxidant N-tert-butyl-o-phenylnitrone (18.9 ± 5.9%), and the 21-aminosteroid U74389G (24.0 ± 3.4%) did not protect the cells. N- Acetyl-L-cysteine even tended to increase cell death (30.1 ± 2.5%, $p = 0.06$). Treatment with MK-801 at the end of hypoxia

did not reduce cell death (23.3 ± 2.3%). In **separate** experiments, a 15-min exposure to 1 mM glutamate without hypoxia did not result in significant cell death (14.7 ± 2.4 vs. 12.2 ± 2.1%, p = 0.07). We conclude that, although somewhat resistant to glutamate toxicity when normoxic, NT2-N neurons die via an ionotropic glutamate receptor-mediated mechanism when exposed to hypoxia in the presence of glutamate. As far as we know, this is the first reported analysis of the mechanism of hypoxic cell death in cultured human neuronlike cells.

L25 ANSWER 19 OF 27 MEDLINE on STN
ACCESSION NUMBER: 1998443272 MEDLINE
DOCUMENT NUMBER: PubMed ID: 9769430
TITLE: Nitric oxide modulates cholinergic reflex pathways to the longitudinal and circular muscle in the isolated guinea-pig distal colon.
AUTHOR: Smith T K; McCarron S L
CORPORATE SOURCE: Department of Physiology and Cell Biology, University of Nevada School of Medicine, Reno, NV 89557, USA.. tks@physio.unr.edu
CONTRACT NUMBER: NIDAA 10793 (NIDA)
SOURCE: Journal of physiology, (1998 Nov 1) 512 (Pt 3) 893-906. Journal code: 0266262. ISSN: 0022-3751.
PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199901
ENTRY DATE: Entered STN: 19990115
Last Updated on STN: 19990115
Entered Medline: 19990106

AB 1. The involvement of nitric oxide (NO) in enteric neural pathways underlying reflex responses of the longitudinal muscle (LM) and circular muscle (CM) layers activated by mucosal stimulation was examined in the isolated guinea-pig distal colon. 2. A segment of colon spanned two partitions (10 mm apart), which divided the organ bath into three chambers: a recording chamber where LM and CM tension was measured; a stimulation chamber where mucosal stimulation was applied; and a middle chamber **separating** them. 3. Brushing the mucosa anal and oral to the recording site evoked simultaneous oral contraction and anal relaxation of both the LM and CM. 4. N omega-nitro-L-argininel-NA; 100 microM) or N omega-nitro-L-arginine methyl ester (L-NAME; 100 microM) applied to the middle chamber or stimulation chamber decreased the oral contractile response of the LM and CM (by about 30-40 %), but increased the anal relaxation (> 600 %) and exposed an anal contraction (> 1000 % increase) of both muscles. The addition of L-NA to the recording chamber reduced the anal relaxation of the LM and CM and the anal contraction of the LM, but slightly increased the anal contraction of the CM. 5. S-Nitroso-N-acetylpenicillamine (SNAP; 10 microM), an NO donor, reversed the effects of L-NA in the middle or stimulation chambers. 6. 1H-[1,2,4]oxadiazolo[4, 3-a]quinoxalin-1-one (ODQ; 10 microM), a soluble guanylate cyclase inhibitor, mimicked the effects of L-NAin the middle chamber or stimulation chamber, but these effects were not reversed by SNAP. 7. The oral contractile responses, and the anal relaxation and contractile responses of the LM and CM produced by L-NA in the stimulation or middle chambers, were blocked by hexamethonium (300 microM) in any chamber. Atropine (1 microM) in the recording chamber reduced the

contractile responses of the LM and CM. 8. In conclusion, endogenous NO facilitates and depresses release of acetylcholine from interneurons in ascending and descending nervous pathways, respectively. These NO effects are mediated through soluble guanylate cyclase in cholinergic interneurons

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ACCESSION NUMBER: 1998410691 EMBASE
TITLE: [Pathogenesis of diabetic neuropathy].
PATHOGENESE DER DIABETISCHEN NEUROPATHIE.
AUTHOR: Ziegler D.
CORPORATE SOURCE: Dr. D. Ziegler, Diabetes-Forschungsinstitut, Heinrich-Heine-Universitat, Klinische Abteilung, Auf'm Hennekamp 65, 40225 Dusseldorf, Germany
SOURCE: Diabetes und Stoffwechsel, (20 Nov 1998) 7/6 (251-266).
Refs: 134
ISSN: 0942-0037 CODEN: DISTF5
COUNTRY: Germany
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 006 Internal Medicine
008 Neurology and Neurosurgery
037 Drug Literature Index
LANGUAGE: German
SUMMARY LANGUAGE: English; German

AB Recent experimental studies suggest a multifactorial pathogenesis of diabetic neuropathy. Most data have been generated in the diabetic rat model, on the basis of which two approaches have been chosen to contribute to the clarification of the pathogenesis of diabetic neuropathy. Firstly, it has been attempted to characterize the pathophysiological, pathobiochemical, and structural abnormalities that result in experimental diabetic neuropathy. Secondly, specific therapeutic interventions have been employed to prevent the development of these alterations, to halt their progression, or to induce their regression despite concomitant hyperglycaemia. At present, the following six pathogenetic mechanisms are being discussed which, however, in contrast to previous years, are no longer regarded as **separate** hypotheses but in the first place as a complex interplay with multiple interactions between metabolic and vascular factors: 1. Increased flux through the polyol pathway that leads to accumulation of sorbitol and Fructose, depletion of myo- inositol, reduction in Na+-K+-ATPase activity and alterations in the expression of several isoenzymes of protein kinase C (PKC); 2. Disturbances in n-6 essential fatty acid and prostaglandin metabolism which result in alterations of nerve membrane structure and microvascular and haemorrheologic abnormalities; 3. Endoneurial microvascular deficits with subsequent ischaemia and hypoxia as well as generation of reactive oxygen species (oxidative stress) and the so called oil, administration of antioxidants (α- **lipoic** acid) to reduce the enhanced formation of reactive oxygen species that induce increased oxidative stress, improvement in endoneurial blood flow and resulting hypoxia by vasodilating agents such as ACE inhibitors and prostaglandin analogues, neurotrophic support by administration of NGF, inhibition of non-enzymatic glycation and formation of AGEs by **aminoguanidine** and immunosuppressive treatment. Since in the foreseeable future (near-)normoglycaemia will not be achievable in the majority of diabetic patients, the advantage of the aforementioned treatment approaches is that they may exert their effects despite prevailing hyperglycaemia. In future,

combinations of certain drugs that produce synergistic effects could be used as therapeutic options.

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ACCESSION NUMBER: 96250090 EMBASE
DOCUMENT NUMBER: 1996250090
TITLE: Cannabinoid receptors are coupled to nitric oxide release in invertebrate immunocytes, microglia, and human monocytes.
AUTHOR: Stefano G.B.; Liu Y.; Goligorsky M.S.
CORPORATE SOURCE: Neuroscience Research Inst., State University of New York, P. O. Box 210,Old West-bury, NY 11568, United States
SOURCE: Journal of Biological Chemistry, (1996) 271/32 (19238-19242).
ISSN: 0021-9258 CODEN: JBCHA3
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 029 Clinical Biochemistry
030 Pharmacology
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English

AB The present study demonstrates that stereoselective binding sites for anandamide, a naturally occurring cannabinoid substance, can be found in invertebrate immunocytes and microglia. The anandamide-binding site is monophasic and of high affinity, exhibiting a K(d) of 34.3 nM with a B(max) of 441 fmol/mg protein. These sites are highly selective, as demonstrated by the inability of other types of signaling molecules to displace [3H]anandamide. Furthermore, this binding site is coupled to nitric oxide release in the invertebrate tissues examined as well as in human monocytes. Interestingly, the cannabinoid-stimulated release of nitric oxide initiates cell rounding. Thus, these cannabinoid actions resemble those of opiate alkaloids. In this regard, we demonstrate that these signaling systems use the same effector system, i.e. nitric oxide release, but **separate** receptors. Last, the presence of a cannabinoid receptor in selected evolutionary diverse organisms indicates that this signaling system has been conserved for more than 500 million years.

L25 ANSWER 22 OF 27 MEDLINE on STN

ACCESSION NUMBER: 96193918 MEDLINE
DOCUMENT NUMBER: PubMed ID: 8641445
TITLE: Evaluation of the relative contribution of nitric oxide and peroxynitrite to the suppression of mitochondrial respiration in immunostimulated macrophages using a manganese mesoporphyrin superoxide dismutase mimetic and peroxynitrite scavenger.
AUTHOR: Szabo C; Day B J; Salzman A L
CORPORATE SOURCE: Children's Hospital Medical Center, Division of Critical Care, Cincinnati, OH 45229, USA.
SOURCE: FEBS letters, (1996 Feb 26) 381 (1-2) 82-6.
Journal code: 0155157. ISSN: 0014-5793.
PUB. COUNTRY: Netherlands
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English

FILE SEGMENT: Priority Journals
ENTRY MONTH: 199607
ENTRY DATE: Entered STN: 19960726
Last Updated on STN: 19960726
Entered Medline: 19960712

AB Here we report that the cell-permeable superoxide dismutase mimetic Mn(III)tetrakis (4-benzoic acid) porphyrin (MnTBAP) inhibits the oxidation of dihydrorhodamine-123 by peroxynitrite, but does not scavenge nitric oxide (NO). MnTBAP protects against the suppression of mitochondrial respiration in J774 cells exposed to peroxynitrite or to NO donors. MnTBAP and N(G)-methyl-L-arginine provide additive protective effect against the suppression of respiration in immunostimulated cells. Our data suggest **separate** contributions of NO and peroxynitrite to the suppression of mitochondrial respiration and support the role of oxidative stress in the expression of the inducible isoform of NO synthase.

L25 ANSWER 23 OF 27 MEDLINE on STN
ACCESSION NUMBER: 96330216 MEDLINE
DOCUMENT NUMBER: PubMed ID: 8760128
TITLE: Nitric oxide alters metabolism in isolated alveolar type II cells.
AUTHOR: Miles P R; Bowman L; Huffman L
CORPORATE SOURCE: Division of Respiratory Disease Studies, National Institute for Occupational Safety and Health, Morgantown, West Virginia 26505, USA.. PRMI@NIORDS1.EM.CDC.GOV
SOURCE: American journal of physiology, (1996 Jul) 271 (1 Pt 1) L23-30.
Journal code: 0370511. ISSN: 0002-9513.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199612
ENTRY DATE: Entered STN: 19970128
Last Updated on STN: 19970128
Entered Medline: 19961203

AB Alveolar type II cells may be exposed to nitric oxide (.NO) from external sources, and these cells can also generate .NO. Therefore we studied the effects of altering .NO levels on various type II cell metabolic processes. Incubation of cells with the .NO generator, S-nitroso-N-acetylpenicillamine (SNAP; 1 mM), leads to reductions of 60-70% in the synthesis of disaturated phosphatidylcholines (DSPC) and cell ATP levels. Cellular oxygen consumption, an indirect measure of cell ATP synthesis, is also reduced by SNAP. There is no direct effect of SNAP on lung mitochondrial ATP synthesis, suggesting that .NO does not directly inhibit this process. On the other hand, incubation of cells with NG-nitro-L-arginine methyl ester (L-NAME), an inhibitor of nitric oxide synthase (NOS), the enzyme responsible for .NO synthesis, results in increases in DSPC synthesis, cell ATP content, and cellular oxygen consumption. The L-NAME effects are reversed by addition of L-arginine, the substrate for NOS. Production of .NO by type II cells is inhibited by L-NAME, a better inhibitor of constitutive NOS (cNOS) than inducible NOS (iNOS), and is reduced in the absence of external calcium. **Aminoguanidine**, a specific inhibitor of iNOS, has no effect on cell ATP content or on .NO production. These results indicate that

alveolar type II cell lipid and energy metabolism can be affected by .NO and suggest that there may be cNOS activity in these cells.

L25 ANSWER 24 OF 27 BIOSIS COPYRIGHT (c) 2004 The Thomson Corporation. on STN DUPLICATE 4

ACCESSION NUMBER: 1996:129341 BIOSIS
DOCUMENT NUMBER: PREV199698701476
TITLE: Effect of selected anti-cataract agents on opacification in the selenite cataract model.
AUTHOR(S): Hiraoka, T.; Clark, J. I. [Reprint author]; Li, X. Y.; Thurston, G. M.
CORPORATE SOURCE: 357420 Biol. Structure, Univ. Washington, Seattle, WA 98195-7420, USA
SOURCE: Experimental Eye Research, (1996) Vol. 62, No. 1, pp. 11-19.
CODEN: EXERA6. ISSN: 0014-4835.
DOCUMENT TYPE: Article
LANGUAGE: English
ENTRY DATE: Entered STN: 27 Mar 1996
Last Updated on STN: 2 May 1996

AB A systematic study of the anti-cataract activity of 14 reagents was conducted using the selenite model. The reagents or their derivatives were identified from literature reports of their potential effectiveness against cataract formation. The effects of each reagent were measured on the phase **separation** temperature, T-c, of lens homogenate in vitro. T-c is a direct measure of molecular interactions leading to protein aggregation. The protective effect of a single subcutaneous injection of each reagent (at a dose of 1.5 mmol (kg body weight)-1) on lens opacification was evaluated in vivo using rats administered weakest effects in vivo were observed with the reagents having the weakest effect on T-c, in vitro. The results were suggestive of a relationship between the effect of a reagent on T-c and protection against cataract formation in vivo.

L25 ANSWER 25 OF 27 MEDLINE on STN DUPLICATE 5

ACCESSION NUMBER: 94138660 MEDLINE
DOCUMENT NUMBER: PubMed ID: 8306087
TITLE: Regional and cardiac haemodynamic effects of NG, NG,dimethyl-L-arginine and their reversibility by vasodilators in conscious rats.
AUTHOR: Gardiner S M; Kemp P A; Bennett T; Palmer R M; Moncada S
CORPORATE SOURCE: Department of Physiology & Pharmacology, University of Nottingham Medical School, Queen's Medical Centre.
SOURCE: British journal of pharmacology, (1993 Dec) 110 (4) 1457-64.
Journal code: 7502536. ISSN: 0007-1188.
PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199403
ENTRY DATE: Entered STN: 19940330
Last Updated on STN: 19970203
Entered Medline: 19940317

AB 1. A series of experiments was carried out on 3 **separate** groups of male Long Evans rats, chronically instrumented for the measurement of

regional haemodynamics, to compare the effects of NG,NG, dimethyl-L-arginine (ADMA) and NG-monomethyl-L-arginine (L-NMMA), and their reversibility by the nitric oxide donors, S-nitroso-N-acetyl-**penicillamine** (SNAP), S-nitroso-glutathione (SNOG), sodium nitroprusside (SNP), and the vasodilator, hydralazine. 2. As previously reported for L-NMMA, ADMA (1-100 mg kg-1) caused dose-dependent pressor and bradycardic effects, accompanied by renal, mesenteric and hindquarters vasoconstrictions. The magnitude and duration of these effects were similar for ADMA and L-NMMA, consistent with their being equipotent inhibitors of nitric oxide synthase. 3. Infusion of SNAP or SNOG (300 micrograms kg-1 h-1) after injection of ADMA or L-NMMA (100 mg kg-1) reversed the pressor but did not abolish the vasoconstrictor, effects of ADMA or L-NMMA. However, a higher dose of SNAP (3 mg kg-1 h-1) caused complete reversal of the pressor and mesenteric haemodynamic effects of ADMA (100 mg kg-1), although its renal and hindquarters vasoconstrictor effects were not abolished. 4. Infusion of SNP (300 micrograms kg-1 h-1) after administration of L-NMMA (100 mg kg-1), caused complete reversal of its pressor and mesenteric and hindquarters haemodynamic effects, and reduced substantially its renal vasoconstrictor action; hydralazine (7.5 mg kg-1 h-1) was almost as effective as SNP in reversing all these variables.(ABSTRACT TRUNCATED AT 250 WORDS)

L25 ANSWER 26 OF 27 MEDLINE on STN DUPLICATE 6

ACCESSION NUMBER: 87049606 MEDLINE
DOCUMENT NUMBER: PubMed ID: 3778868
TITLE: Amino acid specific ADP-ribosylation: substrate specificity of an ADP-ribosylarginine hydrolase from turkey erythrocytes.
AUTHOR: Moss J; Oppenheimer N J; West R E Jr; Stanley S J
SOURCE: Biochemistry, (1986 Sep 23) 25 (19) 5408-14.
Journal code: 0370623. ISSN: 0006-2960.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 198701
ENTRY DATE: Entered STN: 19900302
Last Updated on STN: 19900302
Entered Medline: 19870109

AB An ADP-ribosylarginine hydrolase, which catalyzes the degradation of ADP-ribosyl[14C]arginine to ADP-ribose plus arginine, was **separated** by ion exchange, hydrophobic, and gel permation chromatography from NAD:arginine ADP-ribosyltransferases, which are responsible for the stereospecific formation of alpha-ADP-ribosylarginine. As determined by NMR, the specific substrate for the hydrolase was alpha-ADP-ribosylarginine, the product of the transferase reaction. The ADP-ribose moiety was critical for substrate recognition; (phosphoribosyl)[14C]arginine and ribosyl[14C]arginine were poor substrates and did not significantly inhibit ADP-ribosyl[14C]arginine degradation. In contrast, ADP-ribose was a potent inhibitor of the hydrolase and significantly more active than ADP greater than AMP greater than adenosine. In addition to ADP-ribosyl[14C]arginine, both ADP-ribosyl[14C]guanidine and (2'-phospho-ADP-ribosyl)[14C]arginine were also substrates; at pH greater than 7, ADP-ribosyl[14C]guanidine was degraded more readily than the [14C]arginine derivative. Neither arginine, guanidine, nor **agmatine**, an arginine analogue, was an effective hydrolase

inhibitor. Thus, it appears that the ADP-ribosyl moiety but not the arginine group is critical for substrate recognition. Although the hydrolase requires thiol for activity, **dithiothreitol** accelerated loss of activity during incubation at 37 degrees C. Stability was enhanced by Mg2+, which is also necessary for optimal enzymatic activity. The findings in this paper are consistent with the conclusion that different enzymes catalyze ADP-ribosylarginine synthesis and degradation. Furthermore, since the hydrolase and transferases possess a compatible stereospecificity and substrate specificity, it would appear that the two enzymatic activities may serve as opposing arms in an ADP-ribosylation cycle.

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ACCESSION NUMBER: 1980:185417 BIOSIS
DOCUMENT NUMBER: PREV198069060413; BA69:60413
TITLE: ARGININE DECARBOXYLASE EC-4.1.1.19 OF OAT AVENA-SATIVA SEEDLINGS.
AUTHOR(S): SMITH T A [Reprint author]
CORPORATE SOURCE: RES STN, UNIV BRISTOL, LONG ASTON BS18 9AF, BRISTOL, UK
SOURCE: Phytochemistry (Oxford), (1979) Vol. 18, No. 9, pp. 1447-1452.
CODEN: PYTCAS. ISSN: 0031-9422.
DOCUMENT TYPE: Article
FILE SEGMENT: BA
LANGUAGE: ENGLISH

AB Arginine decarboxylase activity in the shoots of seedlings was high in oats, intermediate in barley and low in rice, maize, wheat and rye. After partial purification, the arginine decarboxylase from the shoots of K deficient oat seedlings was **separated** into 2 fractions, A(MW 195000) and B(MW 118000), by gel chromatography. On gel electrophoresis, the mobilities of these fractions were, respectively, 0.12 and 0.55 relative to bromophenol blue at pH 9.5. Fraction A was twice as active as fraction B in extracts of seedlings grown with both normal and K deficient nutrition, despite the greater activity (+ 5) of the K deficient plants. The properties of the 2 fractions were similar with respect to pH optimum (7-7.5), Km (3 + 10-5M) and the effect of inhibitors. Fraction A was purified to apparent homogeneity by DEAE-cellulose chromatography. The enzyme was specific for L-arginine and it was strongly inhibited by NSD 1055 (4-bromo 3-hydroxy benzyloxyamine dihydrogen phosphate), D-arginine and canavanine. Mercaptoethanol and **dithiothreitol** stimulated the enzyme by approximately 50% and p-chloromercuribenzoate was an inhibitor. Pyridoxal phosphate stimulated activity by approximately 30% and EDTA stimulated activity by 30%. Ca2+ and Mg2+ inhibited the enzyme by 50% at approximately 20 mM. Putrescine and the polyamines showed only moderate inhibition at 10 mM, but **agmatine** reduced activity to 30% at this concentration.

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